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THE CURABILITY OF IDIOPATHIC EPILEPSY

WITH REPORT OF TWENTY-NINE CURES*

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These remarks on the curability of idiopathic epilepsy are made to show that the disease is susceptible of arrest or cure, even in severe and long-standing cases, and also for the purpose of reemphasizing the necessity of depending on an intensive application of the so-called hygienic method of treatment, in contradistinction to the sedative plan of treatment *per se*.

I shall confine my remarks to (1) an analysis of the criteria which should constitute a cure, (2) the presentation of a scheme to follow in using the hygienic plan, (3) the discussion of some of the theories by which cures are brought about, (4) presentation of some of the main reasons why relapses occur, with illustrative cases, (5) the consideration of the question of spontaneous cures, and (6) brief notes of some twenty-nine cases of cures, together with comments on the special features of the individual cases. The clinical notes of the cures are for the most part drawn from my own experience while first assistant physician at the Craig Colony for Epileptics, and from private practice.

Aside from the cases reported in this paper for the first time, there are but few authentic data at hand relative to cured idiopathic epilepsy. There is plenty of evidence, and not a few statements, at hand showing that from 5 to 10 per cent. of idiopathic epileptics are cured, but careful case reports backing these figures do not exist. All of us should look to this defect. Aside from backing the statistical percentage of cures, careful case reports may teach us a more definite and scientific therapy of the disease.

TIME LIMIT FOR CURES

If considerable discussion has arisen concerning the length of time a patient should be free from fits before a cure may be declared, not a little confusion has arisen relative to what constitutes a state of idiopathic

*Read before the American Neurological Association, Baltimore, Md., May 12, 1911.

epilepsy In a general way it may be said that both questions must be settled to the satisfaction of the individual mind All things are relative, several seizures do not constitute a state of epilepsy I have known good trained observers to withhold a diagnosis of the disease even after an extensive series of genuine grand mal covering a period of several years has been in evidence It would seem, however that a common-sense view should obtain regarding the matter Although no nice question whether the cases reported herein are idiopathies or not can be an issue, the occurrence of repeated fits over a period of two years where no adequate organic lesion was present ought ordinarily to suffice to make a diagnosis of idiopathic epilepsy certain

Inasmuch as the time limit constituting a cure in idiopathic epilepsy varies from two to twenty or even thirty years, one needs to formulate some more definite data than a mere time criterion on which one may depend Indeed, it would be far better to eliminate the word "cure" in this connection and substitute the term "arrest" While such a change might, from practical reasons, be undesirable, especially in private practice, one ought to explain to the patients the exact new meaning with which the term is used to designate the more or less uncertain length of time the cure may last and the conditions under which a relapse of the former disease may be expected

CURABILITY

There are not a few clinicians to-day who deny, with their prototypes Esquirol and Delasauve, that idiopathic *grand mal* epilepsy is absolutely incurable and that they have never seen a cured patient A few even deny that the disease is ever really arrested Confronted with a case in instance they take refuge in a denial of the diagnosis Such skepticism is beyond relief

Foreshadowing the simple hygienic plan of treatment of our day, Hippocrates declared the disease curable up to the age of 14 years by proper regimen and change of abode It is necessary, however, he adds, that the mind be normal (not insane and in an absence of the psychic stigma of the disease), and that the body be given to some occupation Suetonius stated that the Roman emperor Caligula was cured of epilepsy during adolescence In modern times Boerhaave and some of his contemporaries and successors believed in the curability of epilepsy Trousseau, writing before the introduction of bromids, believed that in the space of twelve years he had seen twenty cures among 150 patients

While it may never be possible to determine exactly how much spontaneous cure or arrest may figure even in cases under the most intensive treatment, the situation is not without parallel in other adjacent fields of neurology and psychology Spontaneous cures, on account of the natural tendency for self-perpetuation of the disease and the imperfect application

of the hygienic principles rarely occur when there is the slightest stigma of the disease. It may be well doubted that epilepsy can be counted as established in the so-called spontaneous cures which are reported to have taken place at the age of 4 or 5 years The reflex character of simple convulsions at this early age are of too frequent report to warrant so early a diagnosis of established epilepsy It is, however, significant and of moment also to note that in nearly all such cases the hygienic plan of treatment figures largely if not exclusively Spontaneous cures rarely if ever occur between 5 or 6 years of age and the age of 20 years, a period commonly designated both by lay and professional advice in which a patient may be expected to "outgrow" his disease The chances of spontaneous cure improve greatly with advancing years up to 15 years, after which few such cures are noted Ferè, however reported at least four such cases in the forties I have never seen one after 37 years of age One may get histories of spontaneous cures for analysis by obtaining

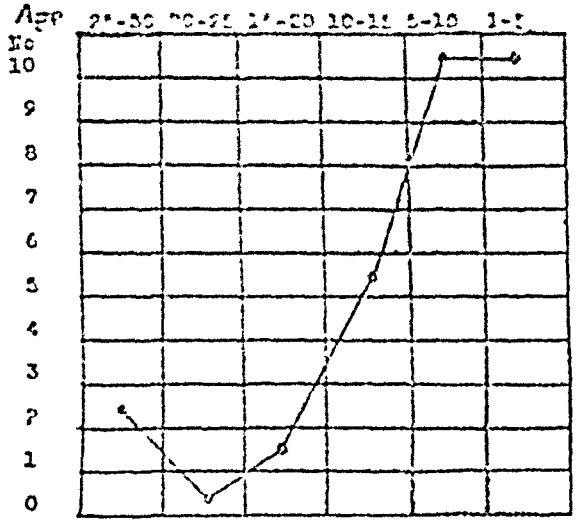

Chart 1—Showing age when fits first occurred in twenty-nine cases

records of such from patients consulting one for affections other than epilepsy and in whose family histories spontaneous cures have occurred Not a few such cases may be studied, especially in epilepsies beginning before the age of 10 years

TREATMENT

In all the spontaneous cures I have been able to study, the careful adoption of some self-applied plan of hygienic treatment is in evidence Probably the favorable termination in many such cases has influenced most epileptologists in planning a broad, rational living plan for his patients under exact medical supervision It is interesting to note, as reports of spontaneous cures decrease in number in literature, cures or arrests under treatment are of more frequent report The fact, no doubt, accounts to some extent for our more optimistic views regarding the curability of epilepsy, a credit to our efforts not fully warranted Maisonnier

saw so-called spontaneous cures in 4 per cent of his patients Heipin had 5 per cent in his experience, and Voisin saw three such cures in 750 cases under his examination Again, Delasauve knew of but two cures in 2,000 cases at the Bicêtre The astonishingly large percentage of the former authors leads one to think that the diagnosis was probably in error I know of but a half dozen such cases in an experience of several thousand Gowers states that true epilepsy developing late in life may sometimes undergo spontaneous cure I have never seen such a case

The time element alone is as worthless as percentages of cures unaccompanied by actual case histories One cannot arrive at anything definite regarding our subject as to the permanency of a cure or arrest without knowledge of the psychical and somatic factors of individual cases being known For instance, not a few writers report cures when the patient has passed but a year or so of freedom from attacks, although the patient still remains under sedative treatment The cured patient must be able to assume charge of his or her affairs, assume the responsibilities of life He should have a true insight into the nature and conditions which brought about the disease He should be able to direct his efforts to ward off the irregularities of life in future In short, a changed mental attitude toward himself and his environment marks the stability of an arrest far more than a mere cessation of fits If the one-time patient does not become tractable and self-regulative I do not hold that the cure will be permanent The irritability must disappear, ambition and proper initiative must return and above all the memory must show decided mending In a physical way the digestion and processes of elimination must approximate the normal even under slight digressions of the diet The individual must not be easily influenced unfavorably by slight lapses in the routine In brief, the stability and normality of the mental and physical health must form a definite part of the criterion as to the permanency of an arrest or cure In such cases with a former history of weekly or monthly attacks and in which an arrest from fits has taken place for a period of two or three years, I count cured patients of epilepsy I do not apply this criterion to patients treated by sedatives In such, a period of several months or even a year may be required to fully eliminate the sedatives from the system The nerve-tissue is remarkably slow in yielding up sedatives such as the bromids, once thoroughly saturated in their use Not infrequently an arrest of attacks precedes a *cure* (in the sense of the criteria laid down in this paper) for a year or more In point of fact, most epileptologists have learned to disregard the continuance of fits in a measure if the other more subtle but pregnant signs of improvement are in evidence The majority of the permanent cures show a gradual subsidence of fits instead of an abrupt cessation It is unfortunate that in this disease the patient who becomes lost to view is

the one most likely to have become cured Such cases are far from rare Such a circumstance has often discouraged similar studies of our subject Arrest or cure is much more likely to be brought about in cases developing before the age of 10 It is well known that little dependence can be placed on the mere word of a patient that he has had no fits for a term of years Therefore detailed histories of cures seem almost inseparable from colony or institutional life But cases drawn from this material should not be a standard of curability of the disease, as the most unfavorable cases are usually sent to these institutions for epileptics

While writers on our subject differ in minor details on the make-up of the principles of the so-called hygienic method or non-sedative plan of treatment, nearly all are agreed that the issues of diet, occupation, recreation and mental training and discipline are the essential components of it

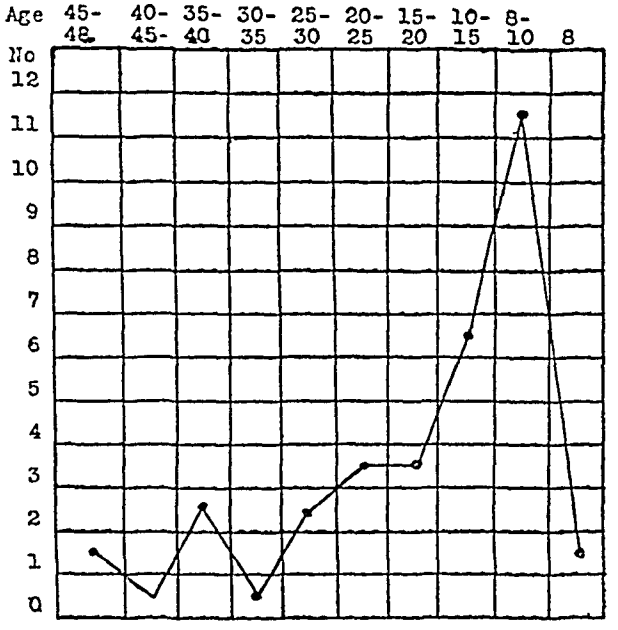

Chart 2 —Ages when the same series of twenty-nine patients were cured

To my mind, the introduction of special medicaments of sedation in the epilepsies has been fraught with more harm than good The sedatives have clouded the issues of causation and prognosis to a remarkable extent They have dislocated and cloaked the errors of metabolism in the epilepsy problem without giving commensurate aid I decidedly take issue with Féré's and Turner's views that the introduction of the bromids has aided the prognosis, especially as regards permanent cures The bromids mask the progress of the disease and make a full understanding of the forces at work in the individual case almost unbelievably complex I have seen many patients treated by sedatives steadily advance in physical, mental and moral deterioration in the face of a steady cessation of fits In not a few the account of a prolonged suppression of fits is squared by an outburst of status epilepticus or a furious maniacal attack Bear-

ing this catastrophe in mind, it is easy to understand the origin of the statement that the bromids easily become "outworn"

When we learn that the bromids are not really curative agents we shall relegate them to a real use (1), as a therapeutic means of determining the severity of the disease with which we have to cope, by determining the sedative level necessary to hold the fits in check, and (2) as adjuvants after all discoverable causes are set right and in such cases needing some small degree of sedation to bridge over expedient periods In cured patients on whom the bromids have been used it would seem that the results are brought about in spite of the bromids rather than because of their use Thanks to a constantly increasing data of anatomico-pathological study in the epilepsies, we now recognize more and more that true epilepsy is a real cortical disorder of which the fits are but one of the psychic incidents, and that the seizures should no longer usurp the whole field of attention with their special and specific therapy of sedation

As regards diet in the cure of the epilepsies, it undoubtedly holds first place in any hygienic system Fully two-thirds of all patients with so-called idiopathic epilepsies show some functional anomaly of metabolism This defect is either congenital or acquired, probably more frequently the former than is commonly supposed In most of my cured patients some defect of this sort persists long after all other factors in causation have been met Indeed in many cases it has never fully returned to the normal although the patient continues diligent in caring for the diet In all my idiopathic epileptics I institute an intensive training and dietetic regimen as thoroughly watched and carried out as though the patients were to enter an athletic contest calling for the highest degree of endurance Usually this scheme, adjusted to individual needs, is placed in the hands of a nurse-trainer who reports to me in daily records of minutest details The trainer lives with the patient and on the same schedule He is the pace-setter No doubt the scheme presupposes an interest on the part of all concerned in the small affairs of life but the results seem to warrant the method At the risk of making the scheme seem commonplace I shall undertake to give a general plan for a typical case, of a young man of 20, who has what I term a metabolic defect as the inciting factor of his epilepsy The example will necessarily seem sketchy but I shall fill in details and explanations at another time

The following is what I understand to be an application of the hygienic method of treatment The patient is placed first of all with a nurse trainer in a congenial but quiet country environment, away from the family by preference The daily schedule runs about as follows The patient rises at 6 a m and takes ten or fifteen minutes of a gradually increasing severe grade of active calisthenics with Indian clubs, medicine ball or weights He then takes a glass of hot water, a cold shower-bath and a brisk rub down, and breakfasts on an egg, small amount of cooked cereal, a glass of milk and some stewed fruit Immediately after breakfast he takes a walk 6 to 8 miles, which he covers in running and walking in about one and a half hours He then takes a glass of milk with or without

raw eggs, and one or two strips of zwieback He is then given a shower-bath and lies down for fifteen minutes He then works at sawing wood or some equally useful occupation until 12 30 He then lies down without undressing, sleeps or not for half an hour and is then given dinner of fish and milk, vegetables, cereals and stewed fruit This meal should be eaten in not less than forty minutes He is then allowed to sleep for one hour, after which he does wood-sawing again as in the morning, and mid-afternoon lunch follows with rest From 5 to 6 p m he is allowed to follow some light intellectual occupation—reading or study Supper of milk, eggs, cereal and stewed fruit is given at 6 30 This meal, as breakfast, is light and should occupy at least thirty minutes in eating The patient is then allowed games, recreation, etc, until 8 30 He then takes the special treatment of a warm bath and general massage, etc, and is in bed for the night at 9 30 No alcohol, tobacco, tea or coffee is allowed The patient is encouraged to drink at least two quarts of water daily High colon irrigations are given every other night until the colitis is reduced, and every ten days castor oil, or calomel in divided doses is given The articles of food in the three-meal-diet are changed every fortnight The occupation is also changed every two weeks if desired The patient is steadily encouraged to work and play at concert pitch, rest complete and absolute is also insisted on No slack or "taking it easy" in the day's program is allowed

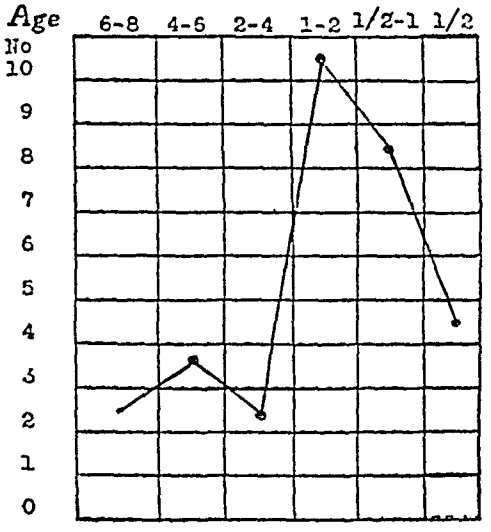

Chart 3—Duration of treatment in twenty-nine cases

A chronological diary report is kept of the day's schedule and is reviewed two or three times a week by the physician For the first few months, a daily urinalysis is made and charted to cover the solids, urea, indican and albumin content Almost without exception, every case showing metabolic defect has either indican or albumin in varying amounts for the first two or three months after coming under treatment In time this entirely disappears if the schedule is carefully maintained consistently For weeks after indicanuria is eliminated, some possible trace of albumin appears in most cases Attempts to analyze the significance of the indican and albumin alternation have not been satisfactory It would seem, however, to be related largely to disturbance in proteid digestion Stool analysis, beyond the grossest examination, has not been of practical service in my experience

The theory by which cures or arrests are brought about is rather unsatisfactory speculation Nevertheless the whole successful plan of hygienic treatment speaks very favorably for the preconceived idea that the disorder in most cases is a metabolic one and a setting right of the

personal habits and plan of living restores the patient to a stationary state equal, if not superior, to his health before the epilepsy began I must say that I have never known a patient not benefited more or less permanently by the plan If grave mental and physical deterioration — especially the former — has already occurred, one can expect only a great betterment or a temporary arrest at best

CAUSES OF THE DISEASE

Most authorities are now agreed that heredity places but little or no bar to recovery My own private and hospital data unmistakably prove the correctness of this view There can be no doubt that the same causes at work in bringing about spontaneous cure are operative in those cases cured under medical care and training This is embraced in the hygienic plan and not to a specific therapy by drugs *per se* In view of this fact the occurrence of relapses in arrests and cures are not difficult of explanation I have never seen a patient either in hospital or private practice undergo relapse without very adequate and obvious reasons Only too often the vigilance of the patient and relatives, the special therapy and the general regimen are suspended or relaxed and the disease recurs Incessant care and attention to these defects are doubly important inasmuch as in those cases in which a relapse occurs the restoration of an arrest again is extremely difficult, the disease is then very stubborn and calls for much more care and training treatment to bring it again to an arrest The nature of the digressions from the personal hygiene is not so glaring in character as some think It is more subtle than the ordinary forms of dissipation of smoking and drinking to excess, the cured patients revert to irregular meals, gluttonous habits and indifferent hours of rest and exercise, especially obvious in the causes provoking a renewal of the disease are mental excesses, excitement and prolonged emotional stress

In an analysis of 138 cases in which the disease was arrested for one year at the Bethel Colony at Bielefeld, nearly a third relapsed, but in this latter number hereditary or alcoholic causes played little or no rôle On the other hand, disturbances in the sexual life such as pregnancies, childbirth and the climacteric were markedly in evidence in the relapsing female patients — all these specific causes are but definite applications of the generic, physical, emotional and mental stress Relapses occur twice as frequently in those cases cured by the use of sedatives

In view of the fact that fully two-thirds of all epilepsies begin under 20 years of age, it is not surprising to know that the number of recoveries occurring after early adult life is small Again, fully two-thirds of all recoveries occur before the disease has existed longer than ten years The apparent curative effects of an intercurrent disease such as an infectious disease, malaria or tuberculosis, are probably mere coincidences

In an analysis of my own data of twenty-nine cases of cures, the arrest of attacks varies from two to seventeen years The age of the youngest patient at time of cessation of attacks was 8 years, and the oldest at 48, the majority were in early adult life The treatment until cessation of attacks was brought about varied from three to eight years The frequency of attacks in the patients varied from several attacks daily to occasional attacks every two or three months. The seizures in all cases occurred both by night and day The age when attacks first occurred varied from earliest infancy to 26 years of age Fully two-thirds of all the cases contracted their disease before 15 years of age Two-thirds of all cases had a well-marked hereditary taint in the make-up, either of epilepsy or insanity or both Not a little light is thrown on the reason why the hereditary epilepsy recovers if one accepts Southard's contention that the hereditary factor is *permissive* and not *mandatory* for the occurrence and continuance of epilepsy in the descendants of neurotic family stock In a general survey of all the cases one can see no special feature

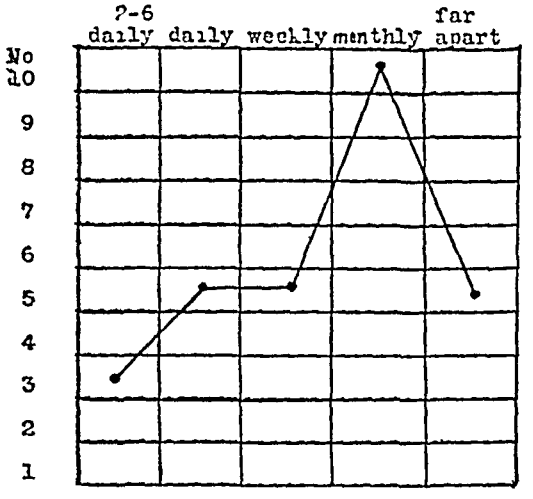

Chart 4—Frequency of attacks in twenty-nine cases

accounting for the presence of epilepsy or its cure in these patients aside from the general statement that there was a faulty physical and mental make-up, congenital or acquired, vicious habits of living attended especially by gross defects of metabolism and chronic dyspepsia and constipation Hence the great value and effectiveness of the hygienic plan of treatment when applied painstakingly and with greatest care

It may be concluded by some that I have not maintained my thesis in view of the care and attention to the health the cured patients are enjoined to observe, and which they for the most part respect A careful analysis, however, will show that the precautions are but those advised by any good sanitarian as a preventive against the recurrence of almost any bodily disorder dependent on a constitutional weakness

If one accepts the primary or secondary diffuse gliosis theory as the epileptic process in the cerebral cortex, we can easily comprehend that

some general toxin in the blood must be the exciting agent provoking these changes The steadily accumulating evidence that epilepsy is a diffuse lesion of the entire cortex is of practical moment and aids much in explaining the complex and bizarre manifestations of the disease It also shows that one cannot pin faith to certain so-called pathognomonic signs in making up a prognosis in an individual case The pathology also steadily repudiates any narrow principles in treatment The most serious pathological bar to recovery in epilepsy lies in the fact that the lesion in the cortex is a destructive one in the cortical elements, the enduring nature of the vast majority of the epilepsies must be thus explained This not only explains the continuance of the fits but many of the permanent physical and mental stigmata of the disease The importance of the most comprehensive and early study of the individual case is obvious The missing links in our knowledge of epilepsy are its pathogenic agents and the structural anomaly of the cerebral cortex which permits the destructive onset of these exciting agents, these two factors still hold anatomico-pathologically the mystery of frequent relapses The gap between the two causative factors is being steadily narrowed by the excellent work being done by a host of workers in this country and abroad In our own country Southard's work needs to be especially studied to be fully appreciated

In closing this therapeutic study of epilepsy, I wish to thank Dr W T Shanahan, superintendent of the Craig Colony for Epileptics, for placing the material of his institution at my disposal and for other generous helps in following the cases after leaving the colony

CASE 1.—Mrs M S, aged 37, married, and has had one bright, healthy child The family history showed a paternal cousin as epileptic, and a paternal uncle had tuberculosis Patient was a delicate child from birth, the second child in line of birth, breast-fed, and a fat baby She suffered much from constipation in childhood The school life was normal, aside from the irregularity of attendance due to easily induced fatigue Jan 6, 1893, she had her first attack, classic grand mal in character, during an attack of indigestion and grip Patient was then 19 years old During the next few days, four grand mal attacks followed An indefinite history was obtained of fainting attacks for eight years (psychic?), following scarlet fever at 6 years of age Patient has always had a congenital slow pulse (48 to 62) She came under my care in May, 1905, with a diagnosis of apparent grand mal idiopathic epilepsy, seizures more or less severe and of monthly occurrence She had chronic indigestion with constipation, aside from this she appeared well and robust The aura was that of a feeling of faintness and the reminiscent aura of Jackson Patient was placed on the hygienic system of control and treatment, and small doses of bromid (30 grains daily) for the first year, after which the hygienic treatment was employed, except 20 grains of bromid daily during menstrual period

Patient has remained well since but for two fainting attacks in 1906 She has been free from attacks of any sort now for four years The pulse rate averages now from 56 to 70 The indicanuria and the chronic indigestion entirely disappeared after the first six months of treatment

Comment.—The case of Mrs M S is an undoubted idiopathic case with a taint in the make up The difficulties in the digestion could also probably be called congenital The patient accumulated endogenous toxins which, together

with physical and mental overstrain, depressed the circulation and precipitated the attacks The depressing effect of the menstrual period also seemed likely to induce attacks on the same general principle Her social position in life made heavy demands on her, her whole routine of daily irregularity of diet, work and rest made it impossible to treat her successfully, the whole living plan had to be changed I believe this patient will remain well so long as she follows a well-ordered plan of diet, exercise and rest All her relatives are persuaded to this view and temptations to break from a well-systematized life will be few

CASE 2—V A S, aged 41, single, occupation, locksmith, came under my care at Craig Colony, Feb 4, 1896 Father died of paresis The patient's grand mal epilepsy began without known cause at 10 years of age At first the attacks were petit mal, only mildly convulsive, in two years they were all grand mal in type At first they occurred weekly, at time of admission they occurred daily, both nocturnal and diurnal, generally the latter The aura was described as a confused and dizzy feeling in the head The patient was dull and stupid and appeared far advanced in dementia Had taken chloral and bromid in large doses No alcohol, tobacco or other excesses in the history The patient showed an irregular heart action, pulse was rapid, soft, and weak He was anemic and poorly nourished, and had the appearance of a weakling He had suffered from chronic indigestion for years independent of taking sedatives

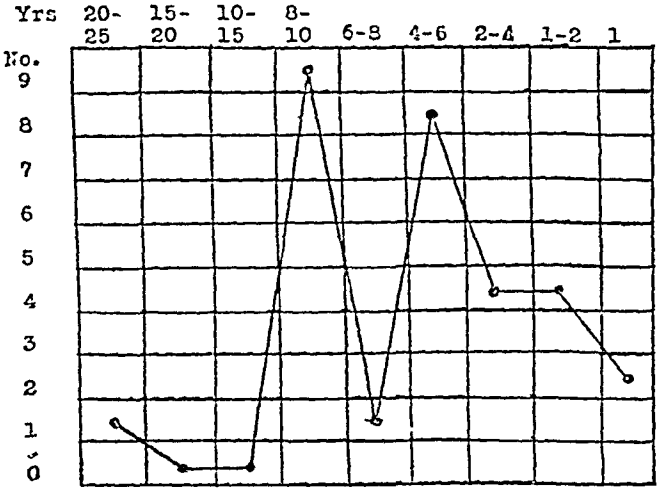

Chart 5—Length of time of cure in twenty-nine cases

The sedatives were steadily withdrawn and the patient gained rapidly in weight and general physical health He had 103 grand mal attacks in the first month, eight or ten in the next month, three the third month and none thereafter He had no attacks after June 12, 1896, and has had none since During most of his residence at the colony, the patient worked steadily in the printing shop and gradually acquired this trade, which he has followed since He has taken the greatest care of his health since, and has led a thoroughly hygienic life, he supports himself and mother The mental state is quite that of the average of his station in life

Comment—This patient was among the first admitted to Craig Colony and was under my personal care throughout his stay there The sedatives were withdrawn in this case not so much from a conviction that they were actually harmful to the patient's disease, but that he was in such poor physical health that a temporary cessation of sedatives was absolutely necessary As is common in such cases, the patient has to pass through a disciplinary course to make a truce with necessity and learn that a well-regulated, systematic life was absolutely essential if he was to remain well To this day he rigidly adheres to this plan and probably in consequence remains a well man No small amount of physical

and mental harm this patient suffered from the injudicious use of bromid and chloral can be gainsaid

CASE 3.—C. W., male, 17 years old, family history of epilepsy, insanity and alcoholism, rheumatism and tuberculosis. Personal history always good. Small pox at 5 and while in the convalescent stage he had a relapse, septicemia set in and multiple abscesses formed. After a prolonged convalescence from the relapse infantile cerebral hemiplegia developed. The convulsions were, however, general and continued for many hours. The next day after the convulsions a left hemiplegia was noticed. The convalescence from his lesion was prolonged, and three months after the initial stroke he had status hemiplegicus unilateralis (left) attended by high fever. There were forty seven grand mal fits in four hours, they all occurred with an order of muscular march, beginning in the left hand, the side paralyzed, as is usual in such cases. He has now grand mal petit mal and psychic attacks of epilepsy every two or three months, two three, and five times daily. The hypertrophy of the left calf on the paralyzed side was first noticed three years ago. The remainder of the left side, however, remains moderately atrophic, true to the usual type or law of infantile cerebral palsy cases. The fits are always followed by a more or less marked exhaustive paralysis in the side most participating in the spasm. The boy is right-handed.

Since the initial report of this case of hemiplegic epilepsy in 1904, as an illustration of hypertrophy in paralyzed parts, the patient has been under constant observation. The treatment has been along the general hygienic lines laid down in this paper. During 1905 he had two seizures, in 1906 he had one attack, none in 1907, and one in 1908. Since this time a period of three years, he has been entirely well. He has gone on with his studies and out-of-door work, and has steadily developed physically and mentally, a fairly robust youth of 17 years.

CASE 4.—M. L. G., female, aged 27, became epileptic at 8 years of age. Attacks were grand mal in type and occurred every two or three months, all were nocturnal without aura. A paternal uncle was alcoholic and an indefinite family history of "neurotic degeneration" was given. There was a definite history of chronic indigestion and constipation and irregularity of life.

The patient was industrious, capable, and well disposed, and followed the hygienic rules closely after admission to the colony, Aug. 1, 1899. No seizures occurred after September, 1900. She has remained well since, a period of over ten years. She earns her own living, at home.

CASE 5.—W. M., male, 29 years old, was admitted to Craig Colony March 17, 1897. His sister died from epilepsy. Patient began his epileptic career at 11 years of age with grand mal seizures without known cause. On an average the attacks occurred weekly. There was an epigastric aura, some perversions of instincts and some criminal tendencies. Physical condition was normal, aside from a corneal opacity of the right eye. Patient was vicious and unmanageable after seizures, otherwise he was contented and industrious.

He was placed on the hygienic standard of treatment and showed marked physical and mental improvement at once. No seizures occurred after Jan. 5, 1898. Patient has been perfectly well since. He is a clerk in a New York City store at present.

CASE 6.—H. H., male, 31 years old. A brother had "spasms." His idiopathic grand mal attacks began when he was 18 years old.

At the time of admission to the colony, Feb. 16, 1900, he had five or six grand mal attacks daily. During the first six months at the colony, patient had over six hundred attacks, the greater part petit mal in character. Patient was given the large doses of bromid mentioned elsewhere[1]. He had no attacks after October, 1900, and has had none since. He has taken no sedatives since leaving the colony, Dec. 2, 1901, and is at present well.

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1. Clark, L. Pierce: Curability of a Rare Form of Nocturnal Petit Mal by the Use of Large Doses of Bromid, Case 2, Am. Jour. Med. Sc., January, 1908.

CASE 7—C M, male, 26 years old, was epileptic since the age of 7 years Attacks of grand mal character occurring weekly, aura of vertigo There was very slight mental impairment at the time of his admission to the colony, Jan 25, 1899, seven years after his epilepsy began Physical examination was negative aside from the fact that he had had rickets and some chest and spinal deformity resulting therefrom Patient was frequently paraphasic after severe seizures

Patient was industrious, well disposed and readily followed the colony life of hygienic treatment Last seizure was November, 1898, and he was discharged as recovered July 17, 1902 He continued at the colony as assistant cook for several years He remains perfectly well at present, twelve years since last attack

CASE 8—M R married female, 32 years old, had grand mal idiopathic epilepsy dating from the seventeenth year The attacks occurred daily She had an aura of seeing some animal approaching, mental state enfeebled, apparently from her epilepsy On admission, Aug 16, 1898, patient was poorly nourished She had suffered from chronic constipation and indigestion for years, also had a chronic cystitis Patient showed great improvement in general and was allowed to go home, Aug 31, 1899 The same patient was readmitted July 16 1900 She was married one week after leaving the colony the first time There was great deterioration physically and mentally during absence from the colony Patient had chronic indigestion and constipation of severe grade, also well-marked tuberculosis of the lungs She had 412 grand mal attacks in 1901 Several times, as a sequence to serial epilepsy, patient had epileptic automatism and delirium Following a strict regime of diet and enforced rest, patient improved steadily physically and mentally No seizures reported since January, 1904, and has had no attacks since

CASE 9—A M B, male, age 53 years, was admitted to the Craig Colony in his fortieth year He had been epileptic ten years at that time, the disease was idiopathic in origin There was but little mental impairment, the aura was visual, balls of fire, etc Attacks were always grand mal and occurred semi-monthly, chiefly by night Patient used tobacco and alcohol to excess since the age of 12, had syphilis at 18 He was a widower with one child

Placed on the colony system of hygienic treatment, he improved rapidly From April, 1898, to April, 1899, he had but four seizures He was very industrious and well disposed and worked constantly at the printing trade which he learned at the colony August, 1899, he had five severe seizures, after which distinct mental deterioration seemed to develop He continued, however, to work industriously at his trade Having shown himself self-supporting on a long parole from the colony and as he had no seizures for three years, he was discharged as cured, June 1, 1903 He has since died of an unknown disease—not that of epilepsy

CASE 10—H W Y, male, aged 18, age at onset of epilepsy, 10 years, was admitted to the Craig Colony, Sept 14, 1904 Father living, aged 36 years, has had epilepsy for two years One brother younger than the patient is living and is well, patient's mother died from tuberculosis Paternal grandaunt of patient is an epileptic, another is insane All of grandparents are living and apparently healthy Father claims the patient was much disfigured after an instrumental delivery He says the boy is very untruthful, causing considerable trouble at times Patient is said to have had no convulsions during infancy and early childhood, although dentition is said to have been difficult, dentition was delayed, it began at 9 months At the end of four years he had frequent attacks of epistaxis Measles at 9, scarlet fever at 10, at which age he had first seizure which was a severe convulsion Second occurred two or three hours later During the past year, he has had a series of seizures every month or oftener, his seizures occurring at the end of a series, being somewhat hysterical in type Aura patient says that he has a sudden tense pain in the precordial region, with vertigo, with a gradual diminution of all sounds and aphasia, severe headaches following

seizures Patient claims seizures are diurnal He sometimes bites his arms after seizures

Physical examination reveals no marked abnormality Sept 26, 1904, patient had a severe seizure which was observed by Dr D L Ross Patient became quickly conscious after contractions ceased Following this he had several similar attacks, some milder in character

Oct 1, 1904, twenty-one grand mal and eighteen petit mal seizures reported since his admission Dec 1, 1904, fifty-one seizures, grand mal predominating, reported during the past month June 1, 1905, attends sloyd school regularly, captain of the junior baseball team Good general health, well behaved Oct 5, 1905 eleven seizures have been reported during the past six months, all of which were grand mal in type and followed periods in which the patient ate quantities of apples and candy On Feb 18, 1909, he was given permission to go home On March 31, 1909, he was discharged as recovered, having had no seizures since April, 1906 A letter from this patient shows that he has been quite well since discharge, a period of recovery of five years

CASE 11.—F W, male, age 14, was admitted to the Craig Colony, July 11, 1907, discharged, July 6, 1910, as recovered The mother of this patient had fainting spells, but is said to have had no convulsions She was excitable by nature, alcoholic and of immoral character, being divorced for adultery Father is living at the age of 46 years, and is said to be a man of good habits The patient claims that he had three sisters and one brother, all of whom died during early life, causes unknown At about the age of 8 years, the patient had his first convulsive seizure Automatism present, no aura Temporal headache for twenty four hours after seizures, which were both nocturnal and diurnal—usually just after arising, average one a month Has never bitten tongue, urinated once during a seizure At some unknown age during early childhood patient is said to have fallen into a cellar, 5 feet deep, hurting the back of his head, but was able to arise immediately and walk home

At time of his admission to the colony, the patient was moderately pale, was fairly well nourished, and showed average intelligence for a boy of his age and station in life When talking, patient showed a tendency to stutter While at the colony, patient assisted with the housework, and attended sloyd as well as day school During a period of from July 1 to Dec 31, 1907, patient had six grand mal and four petit mal seizures, all diurnal During 1908, he had no seizures During 1909 an alleged grand mal seizure was said to have occurred in December No other seizures up to the time of his discharge from the colony, July 6, 1910 He remains well at present

CASE 12.—W H, male, aged 13 years, was admitted Feb 28, 1907 Father died of "spinal meningitis" when 28 years of age Paternal grandmother died at the age of 58 years of some paralysis, same cause assigned for death of maternal grandfather at the age of 39 years Patient claims that his paternal grandmother had epilepsy for twelve years Patient was fed artificially during infancy, pavor nocturnus His first seizure is said to have occurred when he was 11 years old The boy seemed to have a fear of "being killed" He had these both day and night for a period of seven months They then ceased to recur in the day-time Seizures are more severe now with a more marked convulsion Supposed cause was a fall from a wall at a distance of about ten feet The first seizure occurred on the following day, second seizure the day after the first No evidence of any paralysis obtained at time of his physical examination Fairly well nourished, mental condition noted as fair

While at the colony, patient had, during the first year, 180 seizures which were nocturnal and grand mal in type, and 685 petit mal seizures, mostly nocturnal From Jan 1, 1908, he had ninety seven grand mal and 202 petit mal reported In August, 1908, he had one grand mal seizure and from the latter date up to the time of his discharge, April 21, 1910, he had no seizures During the last two years of his residence at the colony, he appeared brighter and

worked in the kitchen at the infirmary and in the doctor's office Discharged as recovered

CASE 13.—M B, male, aged 21 years, was admitted to the Craig Colony Feb 28, 1898 Patient's father is said to have had epilepsy for three years from the ages 17 to 20, when attacks disappeared and did not recur The patient's maternal grandfather committed suicide at the age of 78, maternal uncle died of rheumatism and cerebral apoplexy Patient's mother was insane and died at the age of 58 Patient is the third child in a family of four The first was still-born, second died in convulsions during cholera infantum and the fourth and last child died in convulsions, apparently in status epilepticus At 6 months of age, the patient had several convulsions which were supposed to have been caused by dentition He had scarlet fever and measles at the age of 12, during these illnesses he had no attacks He was troubled by disordered sleep in infancy and had frequent attacks of croup

Attacks occur monthly, of a grand mal type, preceded by an auditory aura and a feeling of dizziness At the time of patient's admission to the colony, his mental state was noted as being fairly good

April 1, 1899 Patient has had no attacks since September 14, 1898, the date of the last grand mal seizure, is in good physical and mental health

October 1, 1899 Three attacks during past six months

October 1, 1901 Patient has been absent from the colony for the past six months and on request of his parents is discharged from the colony to-day, as improved

Readmitted July 26, 1902 His application paper, filed at the time of his readmission, states that he has had seven severe attacks since Jan 1, 1902, two of which occurred on July 18, 1902 While away from the colony he was working on a farm for thirteen or fourteen hours each day He has been careless in his diet He feels as if severely bruised when he has a seizure Same aura of vertigo continues

June 1, 1902 No seizures reported since his readmission

April 1, 1904 Two severe seizures recorded during the past two months Intoxicated once since last note Is a faithful garden worker and in good general health

July 1, 1904 Four seizures during the past three months

Oct 1, 1904 Three grand mal seizures during the past three months

Jan 1, 1905 Patient has had no seizures during the past three months

Feb 28, 1905 This patient, having continued in excellent general health and having had no seizures during the past five months, is to-day discharged as improved and given a position at the colony as a farm worker

March 6, 1911 Still employed at colony and is perfectly well, a period of recovery of seven years

CASE 14.—E D, female, age 24 Mother died of meningitis The epileptic attacks began at 2 years of age, the seizures were always petit mal and occurred in series of several attacks every two or three months without aura Memory rather poor and mind is rather enfeebled In August, 1901, patient had one grand mal attack Her excitability and irritability noted on admission to the colony May 14, 1901, steadily improved under the disciplinary training and hygienic life at the institution She continued to develop, physically and mentally, during her stay at the colony Menstruation began at 16 years of age No attacks are recorded since August, 1901 The patient has remained well since, a period of ten years

CASE 15.—C A W, male, aged 21 Parents were first cousins and father was epileptic Patient's birth was instrumental, had his first attack at 11 years of age He had several attacks daily on admission to the colony April 11, 1902, when 12 years of age There was an aura of vertigo, he suffered greatly from chronic indigestion and constipation It was reported that the patient fell from a table at 2½ years of age, striking on his head, was unconscious for several days and

had convulsions at intervals He had a very severe attack of scarlet fever at age of 6 and had several convulsions at this time Patient was always considered "nervous," and had chorea at 4 years but recovered promptly under treatment At one time he had nineteen seizures in two hours (serial epilepsy)

Patient was unruly and difficult of control for first two years of treatment at the colony After this he became tractable, well disposed and industrious He had no attacks after May 30, 1902, and was discharged *as cured Sept 23, 1906* He has had no recurrence of his epilepsy since, a period of nine years of freedom *from attacks*

CASE 16.—H H, male 23 years of age Patient had convulsions during dentition The epilepsy began at 12½ years, attacks weekly of grand mal and petit mal type occurring always during the daytime Patient had five grand mal seizures within first eighteen hours after admission to the Craig Colony June 19, 1902 He stated he had been free from seizures for two years up to April, 1902 He was quite well behaved and industrious He had twenty-six severe seizures from admission to Nov 1 1902, always occurring in series He had but one grand mal attack during last six months of 1903 and two during the next six months From that time on he made steady physical and mental improvement and was discharged as cured, Nov 9, 1906 No attack since January, 1904 No attacks of epilepsy since, a period of seven years

CASE 17.—C S R male, age 37 years Mother alcoholic and insane, maternal uncle and one brother alcoholic Patient's attacks began at 26 years of age They were grand mal and occurred every two or three months He had used alcohol to excess from 21 to age of 26, the onset of first attack Was irritable at time of seizures Aura of tinnitus aurium After epilepsy began continued to use alcohol in moderation until the date of admission to Craig Colony, Feb 21, 1903

On day of admission he had three seizures He was very nervous but well behaved and industrious and readily followed the hygienic and dietetic regulations of colony life He had two severe seizures in April and two in May, 1903 He continued to have monthly attacks until Aug 12, 1903 Patient has had no attacks since He is a college graduate and a teacher in the New York City public schools He has remained quite well since leaving the colony, a period of recovery of over seven years

CASE 18.—R B N male, age 50 years His epilepsy began with daily attacks of grand mal at 14 years At time of his admission to Craig Colony, April 16, 1903 the attacks occurred only every four or six weeks Occasionally he had an aura of tinnitus, there was no mental impairment Patient was the twelfth child in a family of thirteen children

He had one mild seizure during May, 1903 He was amiable, industrious and well behaved and took to the colony routine and discipline well He had four seizures from July 1 to Oct 1, 1903 No further attacks occurred until the following March, when he had three seizures (1904) He had one severe attack in February, 1905, and none after that date He remains well physically and mentally and has had no attack for a period of six years

CASE 19.—A S, male aged 27 Father and uncle had "spasms," an aunt and brother had chorea Birth of patient was instrumental Patient's attacks were grand mal in type, beginning at 11 years of age They occurred in series of two or three at intervals of a month He had a visual aura of seeing "balls of fire" Seizures were followed by anorexia and vomiting

Notwithstanding the fact that patient followed carefully all the hygienic and dietetic regulations, he continued to have seizures more or less regularly until April, 1904, one year after admission to the Craig colony Patient has since been admitted to the bar and practices law in one of the large cities of the West He is perfectly well to day

CASE 20.—T S, female, aged 19 years Her father was an alcoholic who in an attack of depression committed suicide A sister was epileptic until age of

14, a half-brother was epileptic Patient's attacks of grand mal came on without apparent cause at 5 years of age During the six months prior to admission to Craig Colony, Jan 20, 1904, patient had six grand mal attacks with an aura of vertigo Patient had suffered greatly from chronic indigestion and severe constipation Her birth was premature (seven months)

Patient did well with the colony treatment at the start She had two grand mal attacks in the second month after admission No seizures occurred after March 1905 and patient was discharged as cured Jan 23, 1908 She has remained perfectly well since a recovery of six years

CASE 21.—C E, female, age 44, became epileptic at 21, grand mal type Attacks occurred every two or three weeks, all nocturnal Patient was very irritable before aura but had no true aura, she had slight impairment of memory after epilepsy began The attacks were psychic, very slightly convulsive, at first, but rapidly increased in severity and frequency until they were classic grand mal at 23 Patient had a series of thirteen grand mal and eight petit mal seizures in March, 1901

She had but twenty-three seizures in all while at the colony No seizures since March 1901 she has remained perfectly well since Treatment was only that of the general hygienic type

CASE 22.—R R, female, aged 22 years, domestic Admitted to the Craig Colony July 15, 1898 Seizures diurnal, grand mal Mental status fair, no aura First seizure occurred in September, 1897 Paternal grandmother paralyzed and insane a few years before her death, paternal grandfather intemperate Mother of Irish descent father an Italian of the lowest mental order Twin sisters, now dead, had spinal curvatures The eldest son in the family slightly unbalanced mentally according to paternal aunt A boy next younger than R R is an insane criminal The next, seven years younger than this patient, is epileptic and a patient at the colony The next child a boy, had rickets during infancy but now seems normal The last child, a girl, seems to be normal

This patient, the second child, was peculiar during childhood Did not menstruate until 18 years of age Two or three years previous to this, apparently petit mal seizures Ordinarily she had a good appetite and wanted large quantities of meat

After this patient's admission to the colony, she had no seizures until early in 1899, she had one, which was grand mal in type On April 5, 1899, another attack was reported as grand mal, an attack occurred later in the same year, probably petit mal in character No attacks reported during 1903 and none have been reported up to date This patient is not receiving sedatives, but occasionally, at intervals of months, she complains of severe headache with some dizziness and nausea but no apparent loss of consciousness There is a question as to whether these migrainous attacks have replaced the grand mal attacks formerly observed She is rather irritable and does not get on well with the other patients, with whom she comes in contact

CASE 23.—C C, male, aged 18 years, age at onset of epilepsy, 2 years Admitted to the Craig Colony Jan 22, 1901 Mother epileptic, father insane, two aunts tuberculous Patient, the only child, was a puny baby, fed artificially He had, previous to admission, three or four attacks in a month, both petit and grand mal

At the time of his admission to the colony, his mental state was noted as good During the first year at the colony, he had a grand mal seizure about once a month His last seizure occurred in 1901, no seizure having been reported since that date He has developed mentally and physically in a normal manner He has had no sedative treatment during the past eight years, his epilepsy being apparently completely arrested

CASE 24.—J W A, aged 43 years, onset of epilepsy during infancy Admitted to the Craig Colony Jan 21, 1901 At the time of his admission, it was noted that there was some dementia present, the patient being rather eccentric in his

manner Mother nervous, maternal cousin is said to have had epilepsy Patient is fourth in a family of six children Most of these children had spasms during infancy but they never continued in later life, except in the patient's case During his early years, seizures occurred daily

At the time of his admission to the colony he averaged one or two a week, grand mal and petit mal, with epigastric aura It was noted that he was frequently irascible and in consequence had some difficulties with other patients During the first three months of 1903, he had twenty three seizures, two of which were severe During the next two months, he had twenty-two seizures From July 1, 1903, to Jan 1, 1904, he had twenty-two seizures The last seizure reported for this patient was Sept 13, 1908, since which time he has, so far as can be ascertained, had no symptoms, although it is possible that a mild seizure has occurred and not been reported

CASE 25.—N S, male, 21 years of age, was admitted to the colony April 11, 1902 Mother had fainting spells between the ages of 30 and 35, father was intemperate First attack occurred at 9 years, after an indigestible meal, and was accompanied by vomiting Right side is first and most frequently involved His seizures recurred at first a week or two apart and then every second day, both nocturnal and diurnal, epigastric aura After his admission to the colony he had as many as nine seizures during one month, some mild and others severe July 1, 1903, it was noted that he had forty-four seizures during the preceding three months Jan 1, 1904, forty-two seizures during preceding three months He has had no seizures since late in 1905 Has not been under sedative treatment during the past six years, mental and physical condition have both improved so that, except for some moderate mental impairment, he would compare very favorably with the average epileptic

CASE 26.—E H A, male, aged 32 His father was alcoholic and epileptic, and two brothers died in convulsions, mother and sister died of tuberculosis Patient admitted masturbation and sexual excesses His epilepsy of grand mal and petit mal began at 8 years of age, some mental enfeeblement independent of the onset of his epilepsy His attacks occurred, without warning, every night The description of patient's attacks is given in full in another article[1] Patient was admitted to Craig Colony Jan 26, 1899 Patient was free from epilepsy until 20 years of age, when overwork and irregularity of living brought on two or three grand mal attacks nightly for several months Then there was freedom from attacks for nearly a year, until January, 1899, when he again had many seizures at night from overwork and unhygienic living

The attacks became less frequent as the work lightened, after admission patient kept closely to the dietetic and hygienic life at the colony and improved rapidly In October, 1900, as patient had had a recurrence of rapidly recurring petit mal at night he was placed under large doses of sedatives (200 gr.) daily, he had no more attacks and was discharged Jan 1, 1902, as recovered He was readmitted April 30, 1902, as his seizures recurred again in series of one each night for possibly four or five nights, he then skips a week or ten days without any Under Colony supervision, care and treatment, attacks are diminishing again High dosages of sedatives have not been attended with the first success

CASE 27.—E M C, female, 32 years of age Her epilepsy began at 15 without known cause, attacks of grand mal occurred about once in eight weeks Patient was feeble-minded She was stout and of dwarf stature, had a convulsive tic of the right eye Speech was infantile

She was quite unmanageable and mischievous on admission to the colony Several grand mal attacks soon after admission to the institution, one other attack while at the colony after an interval of two years After this interval, she again had three petit mal and one grand mal attacks in 1910 She is still retained at the colony as an occasional epileptic and probably incurable Attention to hygienic and dietetic rules is compulsory, on account of the enfeebled mental state, otherwise a better prognosis might be entertained

CASE 28—A F M, female, aged 30 Mother neurotic (?) A maternal aunt paralyzed and feeble-minded, one brother intelligent but subject to recurrent melancholia, another brother was rachitic Patient had always suffered from indigestion and constipation, has had goiter since age of 3 Menstruated from age of 12, has always had dysmenorrhea and menorrhagia Patient's seizures began at age of 19 and were grand mal, occurring at almost every menstrual period She was irritable and depressed

Patient had one severe grand mal attack immediately on admission, Feb 25, 1904, after which she improved rapidly physically and mentally and had no more attacks Was discharged as cured 1905, a freedom from attacks for a period of not quite two years Physical condition analogous to that from which she suffered at time of admission having recurred, the epilepsy recurred and patient sought readmission

CASE 29—H W O, male, aged 22 His epilepsy began with several seizures weekly at 11 years of age At time of admission to Craig Colony, Aug 17, 1903, patient had several seizures once a week and several mild attacks daily He was irritable and quarrelsome and frequently automatic, following attacks

He took on the colony treatment very well and improved rapidly The seizures ceased entirely August, 1905, and he was discharged as recovered, Jan 11, 1907 Two years later, after a freedom from attacks for four years, he appeared for readmission, as attacks had returned Unhygienic and irregular living was in evidence in seeking cause for relapse

CASE 30—T B, male, aged 30, was admitted to Craig colony Sept 27, 1904 Age at onset of epilepsy, 16 years Mother had what were termed "nervous convulsions" in 1882 Father and mother living Patient has three brothers and five sisters living, one brother and one sister dead None of the brothers or sisters have convulsions No history of convulsions in other relatives A paternal aunt is insane, one sister at the age of about 19 had chorea for about two years, one brother is an alcoholic Patient as a child was puny, had no convulsions during childhood so far as can be ascertained

His first seizure came on at the age of 16 years, while he was sitting in a chair in a neighbor's house Assigned cause his irregular sexual practices Second seizure followed in about three weeks and for some time after this he had a seizure about every three weeks Seizures have become less frequent and occur now about three or four times a year Last seizure said to have occurred about May 1, 1904 Claims he has never had more than one seizure in the same day Physical examination shows a marked accentuation of the second aortic sound, myopia and hernias Patient was allowed to go home on July 24, 1905, for a visit Having failed to return, he was discharged as recovered He had one seizure in October, 1904 Seizures recurred and he has recently applied for readmission to the colony An irregular and unhygienic life preceded the recurrence of the epilepsy (after an absence of attacks for four years)

CASE 31—M L R, female, aged 30 Patient's uncle and cousin epileptic Patient had her first grand mal attack at 15 years of age, attacks occurred weekly without warning She had always suffered from severe constipation and chronic indigestion

She had been four years epileptic and had had 37 grand mal attacks when placed on the disciplinary treatment and hygienic regulations noted in the foregoing She had but five attacks afterward, each preceded by a breaking down of the routine, the last occurred four years ago The patient has not been under treatment for three years, remains well and is at present in a western college

CASE 32—A B F, female, aged 19 Patient's relatives present a long line of epilepsy and insanity and she is the last member of "two dying families" The epilepsy began when she was 15 years of age, in a series of grand mal attacks without warnings Patient has always suffered from chronic indigestion and constipation The attacks petit mal and grand mal occurred monthly for two years

before being brought under the strictest application of the disciplinary dietetic and hygienic regulations of this paper She has had no attacks in three years and no sedatives in four years She is preparing for college under private tutoring and is a handsome, bright and attractive girl of robust health at present

CASE 33.—A M., male, aged 28. Idiopathic epilepsy began at 12 years of age, the attacks gradually increased in severity and frequency until 16 years of age, when grand mal seizures occurred every two months, petit mal attacks occurred every two or three weeks. There had always existed severe chronic indigestion and constipation.

Patient came under my treatment eight years ago. He was given small doses of bromids in combination with arsenic (Br. 15 gr. t. i. d.) for the first year. Stress was laid however, on thorough dietetic and hygienic regulations which were, and are still maintained. Patient has become entirely well from attacks for over five years. He is an expert in hydraulic engineering and practices his profession in the northwest.

CASE 34.—E. A. L., male, 21 years old. He had three or four grand mal attacks at 11 years of age. The aura was a dizziness and epigastric sensation. Father was alcoholic. There were "teething convulsions" at two years of age.

Patient was at once placed on a strict dietetic and hygienic plan of treatment. At first (six months) patient was placed on small doses of bromid (20 gr. daily). Reliance for the most part was placed on the general plan outlined in this paper. Patient has now been well for thirteen years. He is engaged in stock-raising and fruit culture, and has an extensive plant of his own.

CASES FROM THE LITERATURE

FLOOD'S CASES

1. Young man, a positive epileptic for many years. He was in such condition that he had to give up his teaching profession and practically everything else. His wife took great care of him and after his condition seemed incurable they began rectal injections, very high up, every night, cleaning the bowels thoroughly. He also regulated his diet according to her judgment and made it a point to exercise mildly an hour after supper, taking a bath and going to bed very early. He spent ten hours in bed. This regime he carried out faithfully for about three years without medicine. The attacks diminished and finally ceased. He has been without any attacks for twenty years and has been capable of doing his teaching work.

2. A second case is that of a man who is a veterinary. The attacks came on at the age of 23, although it is a question whether he had not had a few seizures since early childhood. He had grand mal attacks of the worst type for ten years every other day. He often fell out of his carriage and was almost incapacitated. At the age of 33 he began to take belladonna, 6 drops in the morning before breakfast, nux vomica 6 drops before going to bed. In a week's time he had ceased to have attacks. He went nearly eighteen years without any. When I talked with him, he seemed to be perfectly normal, was attending to his duties as a veterinary every day and had a good appreciation of conditions. Two years after he told me of this, I met him and found that his wife had died, he had failed to regulate his diet and had had several more attacks. I have not heard from him since this.

3. A third case is that of a girl of 5 years who had epileptic seizures from childhood. She was a patient at Baldwinville. By taking great care with her diet she kept free from attacks for a month or two at a time. After she ate sugar or candy, she was sure to have a seizure. She was protected as well as possible for three or four years and during that time she had periods of freedom lasting as long as six months. Her family then took her home. She ceased to have the attacks and in a few months began attending school, took up music

lessons and remained free from the seizures for a good many years The last I knew of her, she appeared to be well

4 Severe case, no fits for sixteen years

5 Severe case, no fits for twenty years

TURNER'S CASES

1 Man First fit at 18, treated with bromids four years No return when seen seventeen years later (age 35), but suffered then with neurasthenia

2 Woman, single, epileptic for four years between 28 and 32 Treated with bromids for one year When 54 years old had been free from epilepsy but was suffering from headache and nervousness

HUGHES' CASES

Cases remaining free from epilepsy after twenty years from date of last treatment

1 M B, treated in early childhood, now married and mother of children She and children all free from epilepsy

2 M M treated in early childhood Died recently of pulmonary tuberculosis

3 H M, treated in early childhood, now a mature, well woman Unmarried

4 J H, came under treatment at age of 16, now well and in business

5 R E, came under treatment at age of 17, appeared well for fifteen years, died from railway accident

6 J H O, came under treatment at age of 30, free and in business twenty years later

7 Capt McK Mere statement of twenty-year cure

8 W G B, stationer Cured after twenty years Mature when attacked

9 Male, was treated in 1859 and attacks never returned afterward Became a letter carrier Age at beginning of attacks not stated

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A CRITICISM OF THE USKOFF SPHYGMOTONOGRAPH*

JOSEPH ERLANGER, M D
ST LOUIS

The physiology and pathology of blood-pressure in man have excited the interest of a large number of workers for a great many years and without any apparent abatement The contributions to the subject have been many, new forms of instruments are constantly being devised, new criteria for the determination of the pressures have developed, and extended observations on the pressures in physiological and pathological conditions have been published In many places blood-pressure observations are now made as a matter of routine In consequence of this activity, many persons who are not in a position to question the value of instruments, or to analyze critically the data they are said to afford, are called on to use instruments and to interpret results obtained therewith It is, therefore, essential, in order to spare the time of the routine investigator and to prevent the appearance in the literature of numerous articles based on false premises, to direct attention as soon as possible to descriptions of faulty instruments and to unjustifiable generalizations which from time to time must necessarily find their way into the literature

The primary object of this communication is to call attention to a physical defect in the Uskoff sphygmotonograph This instrument was first described in detail in 1908[1] I did not, however, have an opportunity to work with an exemplar of it, nor did I have have access to the journal in which it was described, until 1910 And it was only during the past year that I have had the opportunity of making the experiments herein recorded Indeed, it was hoped, but in vain, that this criticism might come from another pen

It is not necessary to describe the sphygmotonograph in detail, for this the reader is referred to the original description Essentially, it is a sphygmoscope, air being the medium of transmission By means of the usual sphygmomanometer cuff the pulsations of the brachial artery are transmitted under controllable pressures to a rubber bulb This rubber bulb is enclosed in an all but air-tight space (Fig 1) Consequently any changes in the volume of the former, due to pulsatile and other changes of pressure within it (in the so-called pressure-space), alter the pressure in the latter, the tambour, space These pressure changes may then be

*From the Physiological Laboratory of Washington University

1 Uskoff Ztschr f klin Med, 1908, lxvi, 89, also Russk Vrach, 1905, No 37

recorded on a moving smoked paper by means of a tambour In order to obviate the effect on the tambour of the slow, but large, alterations of pressure that are produced by the manipulation of the pressure within the pressure space, and still leave practically unimpaired the effects due to the more rapid pulsatile variations it is desired to record, a permanent but very small communication is made between the tambour space and the exterior

It will be seen that in these respects the Uskoff instrument is the counterpart of the Erlanger sphygmomanometer, which was described in 1902,[2] of the existence of which Uskoff does not seem to have been aware There is, however, one very essential difference between the Uskoff and the Erlanger instruments in the part of the mechanism that has been described above the rubber bulb in the Uskoff instrument is protected from expansion due to internal pressure by a surrounding silk meshwork, whereas in the Erlanger instrument the rubber bulb is free

With the first opportunity I had to use the Uskoff instrument, I became suspicious of the effect the meshwork might have on the performance of the instrument It is here necessary to remind the reader that in making a blood-pressure estimation, the pulsations are recorded while the pressure in the instrument is falling Now, it could be seen that, with such pressures as are necessary to start all estimations, the rubber bulb completely fills the surrounding meshwork and bulges into its spaces At these pressures, therefore, the rubber bulb is supported by the mesh When the pressure is permitted to fall, as in making estimations of the blood-pressure, it could be seen that at a pressure in the bulb of about 100 mm Hg the wall of the rubber bulb begins to recede from the meshwork, while it was only at a considerably lower pressure — one which was difficult to determine by mere inspection — that the rubber bulb begins to swing entirely free of its support It was obvious that at least two, possibly three, moduli of elasticity come into play, namely (1) that of the rubber supported by a rigidly stretched silk meshwork, (2) that of the rubber supported by a silk mesh not quite rigidly stretched (relatively unimportant), and (3) that of the rubber entirely unsupported

In order to learn whether these inferences from inspection were correct, as well as to ascertain their significance, it became necessary to determine by methods entirely free of the uncontrollable factors that always obtain under the conditions of blood-pressure observations whether, and by how much, this instrument deviated from the simple law of extensibility This was accomplished, among other ways, by measuring the relative volume changes of the Uskoff bulb when subjected to equal decrements of internal pressure

2 Erlanger Proc Am Physiol Soc, Am Jour Physiol, 1901-1902, vi, p xxii Also Johns Hopkins Hosp Rep, 1904, xii, 53

The apparatus that was devised for this purpose is shown schematically in Figure 1 The rubber bulb, A, with its meshwork (one of the two openings in the bulb was permanently closed) is suspended freely in a tightly stoppered bottle, B The interior of the bulb is in communication with a mercury manometer, C, with a pump, D and with the exterior through the stop-cock E By forcing air, by means of the pump into the bulb system the pressure within it could be raised to any desired point and could be held there by closing the stop-cocks, E and F This pressure was indicated by the manometer The pressure could be lowered by permitting air to escape through E All of this system with the exception of the bulb was as inextensible as it was possible to make it The bottle, B, was in communication with the horizontal glass tube, G, in which was placed a bead of water, H, and with the exterior through the stop-cock, I With I closed any change in the volume of the bulb A, caused the water bead H to traverse a corresponding volume in the

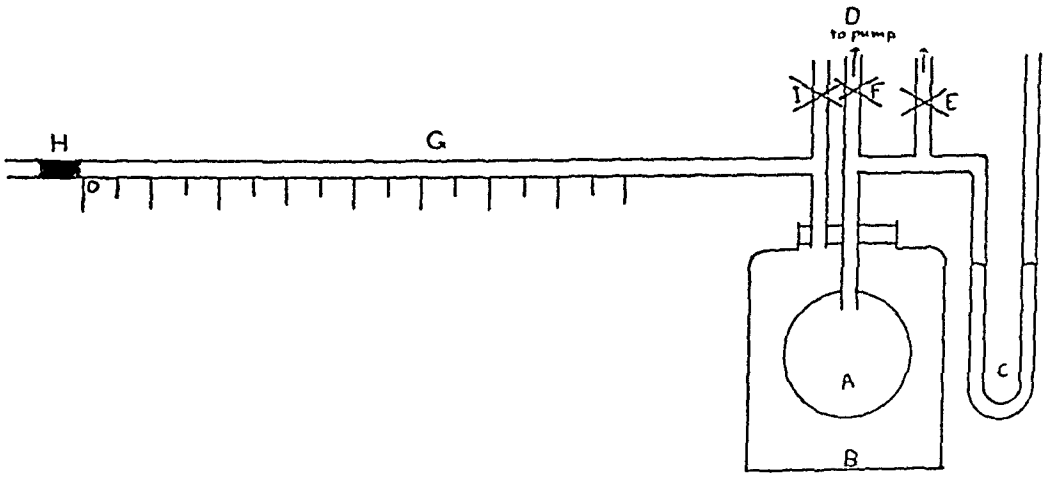


Fig 1 —Diagram of the apparatus employed for the purpose of measuring the extensibility of the rubber bulbs For description see text

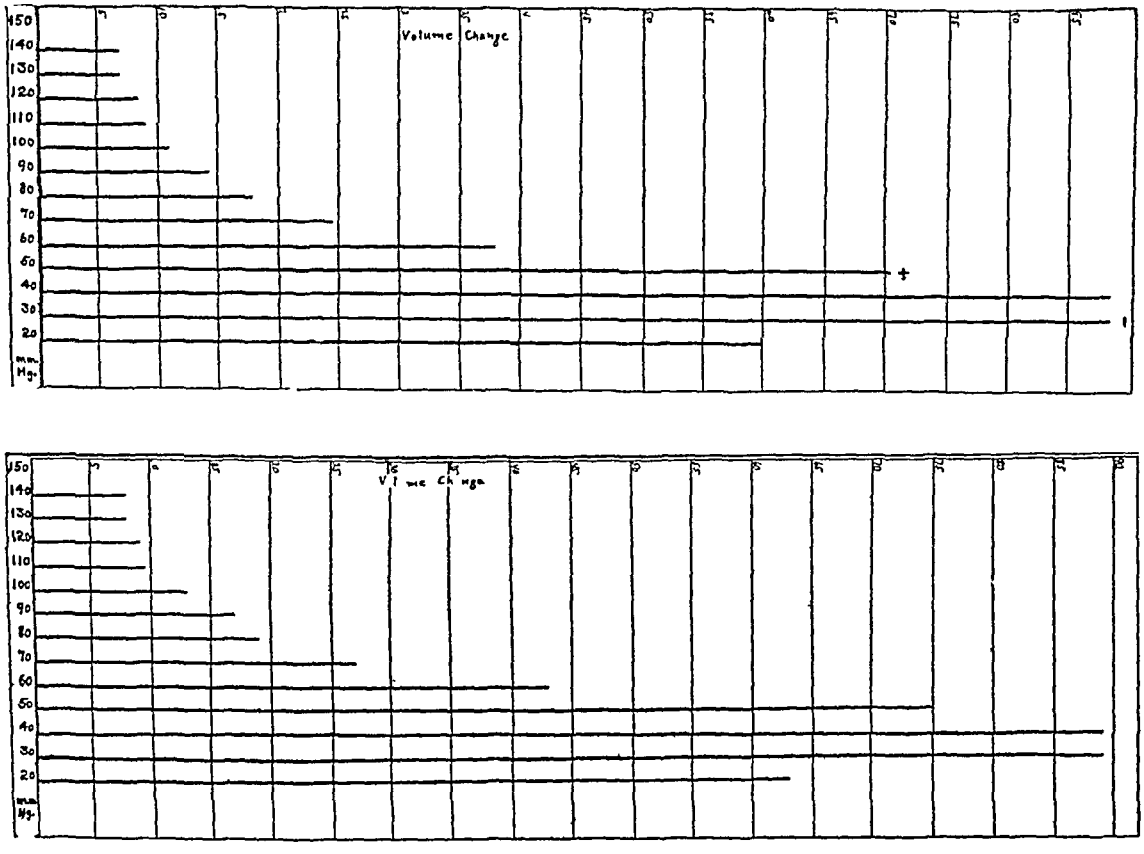
tube, G In this way, had the tube, G, been calibrated, it might have been possible to measure absolute volume changes As, for the purposes of this investigation, a knowledge of the relative volume changes was all that was necessary, the measurements were made as follows A scale was laid under the tube, G, and by means of the communication, I, the water bead was brought to zero before each decrement of pressure The length of the tube traversed by the bead during each decrement was, therefore, a relative measure of the volume change of the bulb

The experiment was performed by raising the pressure in the bulb to the desired starting point, 150 mm Hg in most of the trials, then bringing the bead, H, to zero, and, with I closed, permitting enough air to escape through E to lower the pressure 10 mm Hg The position of the bead, H, was then read, when H was again brought back to zero and the pressure permitted to fall through another 10 mm Hg, and so on

Attention should be called here to two difficulties in the way of obtaining exactly concordant readings with this apparatus

1 The actual change in the level of the meniscus of the mercury manometer being only 5 mm , there was always a possible error of 0 5 mm in the reading, of at least 10 per cent

2 The size of the bead, as a rule, decreased as it traversed the tube from zero This, it will be seen, only tended to minimize the error of the Uskoff bulb It is hardly necessary to add that ordinary precautions were taken to keep the temperature of the air in the bottle, B, constant, and, in any event, the time consumed in making a single reading was so short that such slight temperature variations as might have occurred were



Figs 2 and 3 —Showing the relative volume-changes of the Uskoff bulb with successive pressure decrements of 10 mm Hg The length of the horizontal lines indicates the volume-changes associated with the decrements of pressure to the values over which the lines are erected

certainly negligible Furthermore, the readings in successive observations have been so concordant that there could be no question as to any serious error due to temperature variations The Uskoff bulb, on which these observations were made, was obtained through the dealers in this country

The results of the tests are shown graphically in Figures 2 and 3 The length of tube traversed by the bead, i e , the relative change in volume of the bulb with successive decrements of pressure amounting to 10 mm Hg, is indicated by the length of the corresponding lines It

will be seen that decrements of 10 mm Hg between 150 and 130 mm Hg cause a change in the volume of the bulb of the magnitude of 7 or 8 The changes of volume then increase, slowly at first and then, at about 90 mm Hg. with extreme rapidity, until the pressure has fallen to about 40 or 30 mm Hg, after which the volume changes diminish

Obviously the Uskoff bulb does not obey the simple law of extensibility, its extensibility, as was apparent from the outset, is undoubtedly modified by the factors above referred to (see test of free bulb)

Now, how would a bulb with these physical characteristics affect the readings of the instrument as a whole? The answer is obvious The pressure-changes in the tambour system are proportional to the volume changes of the rubber bulb in it, and, roughly, the excursions of the tambour head are proportional to the pressure-changes in the same system Illustrating this proposition by means of two extreme figures if a pulse-pressure that effects within the pressure space a pressure change of 10 mm Hg between 140 and 130, produces an excursion of the tambour head amounting to 1 mm , then a pulse-pressure effecting the same change, but between 50 and 40, would move the tambour head through

$$\frac{1 \times 87}{7} = 12.4 \text{ mm}$$

That is to say, the instrument at the latter range would be about twelve times as sensitive as at the former It is hardly necessary to add that this is only a very rough approximation There are so many factors that may affect the amplitude of swing of the recording lever, such as varying tension within the tambour with varying pulse amplitude, varying fling of the lever with variations in the amplitude and form of the oscillation, etc , that it is quite impossible to arrive at anything more than a rough approximation Such details are, however, unimportant The essential point is that an instrument, the reading of which depends on changes of amplitude of a recording lever effected by the operation on it of forces from without, should transcribe these forces in their true relative amplitudes The Uskoff instrument evidently does not do this

The next question to be answered is Does the large inherent defect in the Uskoff instrument render it altogether unfit for blood-pressure estimations? There can be no doubt but that it does The readings of the blood-pressures, both systolic and diastolic, with this instrument, depend on changes in amplitude of recorded pulsations The instrument, if acted on by a pulsatile force that did not vary during the whole range of fall of pressure, would of itself yield a record whose outlines would be those of Figures 2 and 3 This form of record is such as might be obtained from a human subject with an instrument equally sensitive at all pressures, it is a record that would be given by a subject having systolic and diastolic pressures in the vicinity of 120 and 30 mm Hg,

respectively Furthermore, each instrument will have its own curve of inherent sensitiveness, since the latter is dependent on factors that are largely beyond the control of the manufacturer, namely, the extensibility of the rubber bulb, the relative diameters of the encasing meshwork and rubber bulb, the rigidity of the meshwork, and the size of its meshes Every instrument, then, has its personal question which must add itself algebraically to the effect produced from without It is obvious that even if the personal equation could be determined for each instrument, it would be far too large, and the calculation far too difficult to warrant the making of the proper correction of each estimation

What do actual tests of the instrument in blood-pressure estimations show? Such tests may be of two kinds (1) a comparison, in an animal, of the readings made with the Uskoff instrument and direct readings of the blood-pressure in an artery, and (2) a comparison of readings made simultaneously on the same human subject with the sphygmotonograph of Uskoff and some other blood-pressure instrument of tested accuracy

The first method has been employed by Uskoff himself He found the diastolic pressure, as determined with his instrument, to be from 0 to 20 mm Hg higher than the actual diastolic pressure Although this error is greater than it should be, it is not in itself prohibitive, since in animals it is difficult to get accurate indirect values through the cuffs that must be employed for the transmission of the pressure to the leg Of greater significance is the fact that the average error, as determined by Uskoff, is greater with relatively low than with relatively high diastolic pressures Thus, we have averaged, on the one hand, the errors of all his estimations in which the diastolic pressures were 100 mm Hg or over (see his table,[1] p 102) and, on the other, all of the errors in which the diastolic pressures were under 100 mm Hg, and obtain for the former, 7, and for the latter, 12 In view of the fact that the lowest diastolic pressure in Uskoff's table is 92 mm Hg, a pressure at which, with falling pressures, the fault in the instrument is just beginning to manifest itself (Figs 2 and 3), it seems justifiable to state that the difference would have been even greater had Uskoff encountered lower pressures in the course of his research It should be added at this point that the error due to the resistance offered by the tissues increases with the pressures they are called on to transmit to the artery With a perfect instrument, therefore, the error would have been larger at high than at low pressures, just the reverse of the results obtained by Uskoff

How do readings of the Uskoff sphygmotonograph compare with those of some thoroughly tested sphygmomanometer, when they are made simultaneously in man? I have made a few tests of this nature with my sphygmomanometer Although the results are in keeping with the foregoing discussion, they will not, for obvious reasons, be used here It is preferred to quote instead the results of other investigators

Fantus and Staehelin[3] have compared the readings of the Uskoff instrument with the Recklinghausen tonometer Apparently only one test was made and the two readings were made one after the other, not simultaneously They assert, however, that the blood-pressure did not change in the interval The test showed that the largest oscillations of the Uskoff instrument are higher relatively, than the smaller oscillations They found, in addition, that "in the curves of the Uskoff apparatus neither the sudden diminution nor the change in type of the separate strokes can be recognized" On the other hand, "maximum oscillations occur at the same pressure as with the other form of apparatus" In other words, the sudden diminution in amplitude (their figure shows this to have occurred at 80 mm Hg, i e just where the error of the bulb is most apt to manifest itself), which is generally believed to indicate the diastolic pressure, we do not doubt, was obscured by the increasing extensibility of the Uskoff bulb at this point The fact that the maximum oscillation of the two instruments in this test occurred at the same pressures is not unexpected since they were recorded at a time when the pressure was high enough, 110 mm Hg, to be practically above the region of error (see Figs 2 and 3)

Fantus and Staehelin[3] attributed the difficulty to a totally different factor, namely, the presence of the capillary opening in the tambour of the Uskoff instrument They did not, however, make any attempt to determine by means of direct experiment whether the elimination of the capillary opening would eliminate the difficulty That the capillary opening is not the cause of the absence of the sudden diminution in amplitude is proved by the presence of this important mark on the records of other instruments that make use of this device, as well as by experiments which have shown that such an opening, if sufficiently small does not materially modify the form of a blood-pressure record[4] On the contrary, the capillary opening, did it act as Fantus and Staehelin premise, namely, to reproduce the larger and more rapid pulses in relatively larger amplitude, would tend to exaggerate, rather than to obscure this sudden change in height of oscillation[4]

Van Westenrijk[5] has compared the readings of the Uskoff sphygmotonograph and of the sphygmoscope of Pal with those of the auscultatory

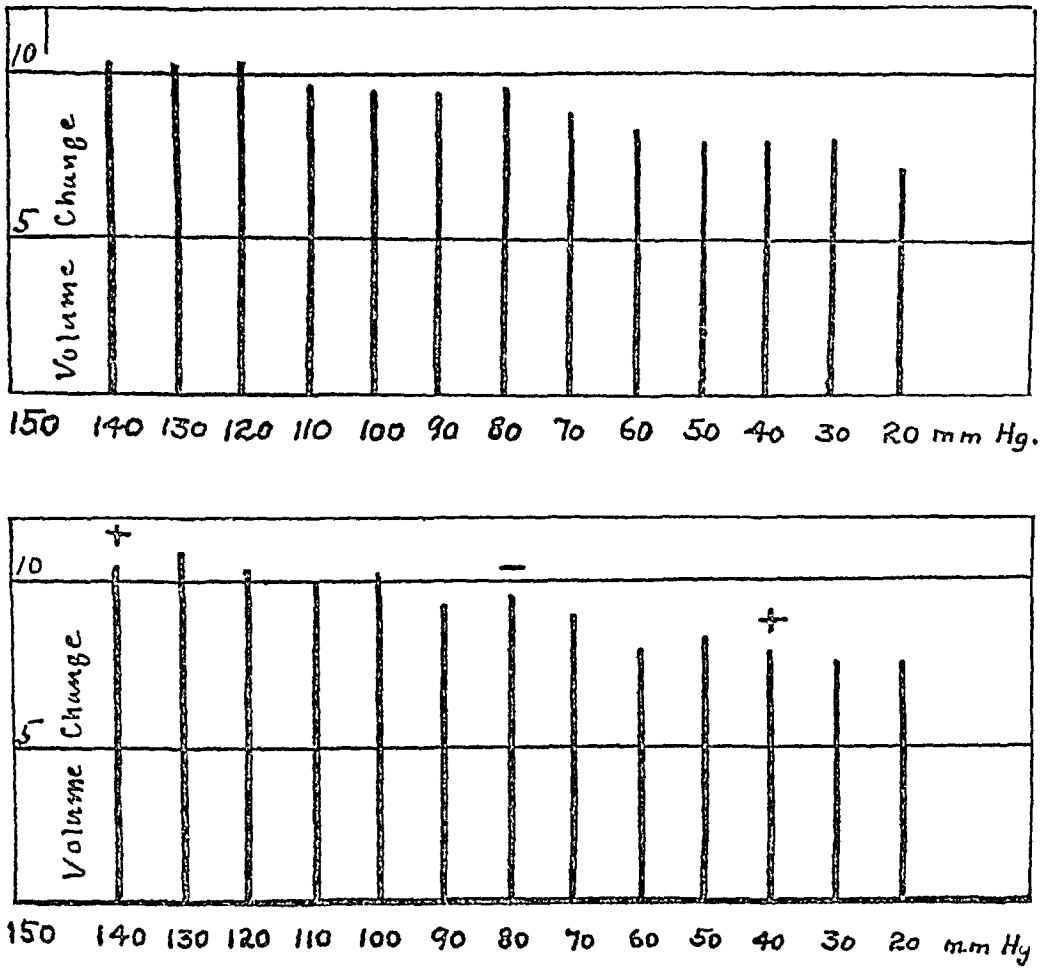
3 Fantus and Staehelin Ztschr f klin Med, 1910, lxx, 444

4 I am inclined to believe that the negative results recorded by Fantus and Staehelin are, in part at least, to be attributed to the use of an instrument which even according to their own observations, is faulty In any event, their conclusion to the effect that "exact investigations of the blood-pressure after muscular exercise show that in the healthy the regulation of the blood-pressure is too complicated to permit of the drawing of any conclusions from the maximum and minimum blood-pressures and pulse amplitude," is not concurred in by other investigators using other forms of blood pressure apparatus (e g Lowsley Am Jour Physiol, 1911, xxvii, 446)

5 Van Westenrijk Ztschr f klin Med, 1908 lxvi, 465

method of determining the blood-pressure He could find no constant correspondence between the pressure at which maximum oscillations were obtained with the Uskoff instrument and the pressure at which the sounds in the artery disappeared On the other hand, there was an almost exact agreement between the significant pulsations of Pal's sphygmoscope and the significant sound phenomena as revealed by auscultation of the artery distal to the compressed area

Van Westenrijk makes no attempt to account for his difficulties with the Uskoff instrument, they, however, receive a ready explanation in the light of the defect herein described



Figs 4 and 5 —Showing the relative volume-changes of the unsupported rubber bulb with successive decrements of 10 mm Hg Units on the ordinates have the same value as those indicated on the ordinates of Figures 2 and 3

The tests of the Uskoff bulb were naturally checked by similar tests of an unenclosed rubber bulb As the unsupported Uskoff bulb cannot sustain the pressures it is necessary to work with, a bulb from an Erlanger sphygmomanometer was employed in making these tests The results of two of the many experiments made are shown in Figures 4 and 5 These are on the same scale as Figures 2 and 3 If we except the slight variability due to the experimental error, it is seen (1) that

the amplitude of the volume changes occurring at pressure below 110 mm Hg are smaller than those of the Uskoff bulb, and (2) that the extensibility diminishes steadily (from 10 5 to 8, approximately), as the basal pressure decreases from 150 to 20 mm Hg This diminution in amplitude is due to the change in the volume of the bulb, the area acted on by the pressure being larger in the more than in the less distended bulb Provided the limit of elasticity is not exceeded, and providing the extensibility is not too great, the curve of sensitiveness of the free bulb will always have approximately the same relative form In any event, the changes in sensitiveness under different pressures are so slight compared with the oscillations produced by the pulse, and so constant, that they would not in any way interfere with the interpretation of a blood-pressure record The Uskoff bulb, it should be added, shows the same decrease in extensibility, and in far greater degree relatively, when, at low pressures (20 mm Hg), it is free of the meshwork

And in regard to the first difference mentioned above, the small amplitude of the unsupported bulb is the price that must be paid for a rigidity that is sufficient to obviate the necessity of a supporting meshwork

The results of this investigation would naturally suggest substituting the supported bulb in the Uskoff instrument by an unsupported bulb This, however, is impracticable, at least with the form of tambour and lever at present employed by Uskoff This conclusion is based on a comparison of the amplitude of the records obtained from one and the same subject with an Uskoff instrument and with an instrument (the Erlanger sphygmomanometer) containing an unsupported bulb To cite just a single illustrative case, the maximum amplitude with the former was 9 mm as compared with 21 mm , the maximum amplitude with the latter , this, despite the fact that the extensibility of the Uskoff bulb at its optimum is almost ten times that of the unsupported bulb Whether or not the recording mechanism of the Uskoff instrument could be made sufficiently delicate to render possible the use of the unsupported bulb was not within the scope of this research to determine

At pressures above 120 mm Hg, the oscillations of the Uskoff instrument are apt to be very small, so small that the employment of the change of form of the recorded wave as a criterion of the systolic pressure[6] was usually quite impossible, while the employment of the sudden increase in oscillation for the same purpose was often precarious

At this point should be considered the criterion for the estimation of the systolic pressure, described by Uskoff in his paper Uskoff states that systolic pressure is indicated, with falling pressure, by the "beginning of oscillations" Without entering into a detailed discussion of this

6 Erlanger Am Jour Physiol , 1908, xxi, 24

matter, it will only be necessary to recall here the papers of Roy and Adami published in 1890,[7] in which the proof is furnished that the pressure at which the first oscillations occur depends primarily on the delicacy of the recording mechanism With a pressure on the artery sufficient to occlude it completely throughout the entire sphygmic cycle, the hydraulic ram action of the pulse on the upper conical closure of the artery usually effects oscillations of some magnitude I have obtained oscillations at pressures on the arm that were twice the systolic pressure. And, as a matter of fact, the records published by Uskoff contradict his own statement, they show oscillations for some time before the place where are inscribed the marks indicating the position at which the pressure was systolic

Some of the ingenious devices employed by Uskoff in his sphygmotonograph should not be passed unnoticed. The levers writing horizontally, such as were employed by Dudgeon on his sphygmograph, could they be made sufficiently delicate, would have decided advantages over vertically writing levers, especially when, as in polygraphic work, it is necessary to manipulate more than one recording device The device for automatically marking on the record the rate of fall of pressure is extremely ingenious Excepting, however, the first observations of a beginner, or investigations demanding unusual accuracy and freedom from personal equation, a record of the rate of fall of pressure seems to be superfluous When it is necessary it can readily be obtained, as has frequently been done, with a recording electromagnetic signal, such as is to be found in every laboratory, by closing the key with each decrement of 5 to 10 mm of mercury.

1806 Locust Street

7 Roy and Adami Practitioner, 1890, xliv and xlv

INFANTILISM IN PITUITARY DISEASE

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Since the appearance of Frohlich's paper[1] in 1901, it has become generally recognized that tumors in or near the pituitary gland may cause disturbances of body growth and general metabolism which are quite distinct from acromegaly and gigantism Frankl-Hochwart[2] has recently collected and analyzed the findings in 155 pituitary affections of this character The symptoms present may be roughly divided into two classes those due to the mechanical effects of the tumor and those which seem to be due to an altered internal secretion To the former group belong the headache, vomiting and visual disturbances The most characteristic of these, primary optic atrophy and unilateral or bilateral temporal hemianopsia, are due to direct pressure on the optic chiasm or nerves To the latter group belong the sexual disturbances (retarded sexual development, cessation of menses, etc), the obesity, the stunted growth, and possibly the occasional diabetes insipidus These are due, in part at least, to a diminished secretion of the anterior lobe of the gland (hypopituitarism) [3]

REPORT OF CASES

Owing to the general interest in this group of conditions and to the fact that they are probably more common than is generally supposed it seems advisable to report the following case histories, even though the diagnoses were not confirmed at autopsy or operation The clinical pictures presented by the first two patients are so characteristic as to leave little doubt concerning the nature of the trouble The third, a doubtful case, is reported because the effect of lesser changes in the pituitary secretion is but little understood and because it is probable that in this patient we are dealing with a mild form of chronic hypopituitarism

CASE 1.—*History of brain tumor Blindness due to primary optic atrophy Retarded growth Sexual infantilism Obesity Diabetes insipidus*

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*From the Department of Internal Medicine, University of Michigan

* Read in the Section on Practice of Medicine of the American Medical Association, at the Sixty-Second Annual Session held at Los Angeles, June, 1911

1 Frohlich, Alfred Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie, Wien klin Rundschau, 1901, xv, 883, 906

2 Frankl-Hochwart, L, v Die Diagnostik der Hypophysistumoren ohne Akromegalia, Wien med Wchnschr, 1909, lix, 2127, 2258, 2326

3 Cushing, H Partial Hypophysectomy for Acromegaly, Am Surg, 1909, cl, 1002, Biedl, A Innere Sekretion, Berlin and Wien, 1910

History—The patient was a young man, aged about 27, family history negative Between the ages of 5 and 9 years he had the typical symptoms of brain tumor, with severe headaches, vomiting, marked emaciation, and gradually developing dimness of vision which progressed to complete blindness At this time also he began to suffer from polyuria At about the age of 9 the headaches and vomiting disappeared, the patient began to increase in weight, and since that time he has been excessively fat He has never shown the slightest indications of sexual development

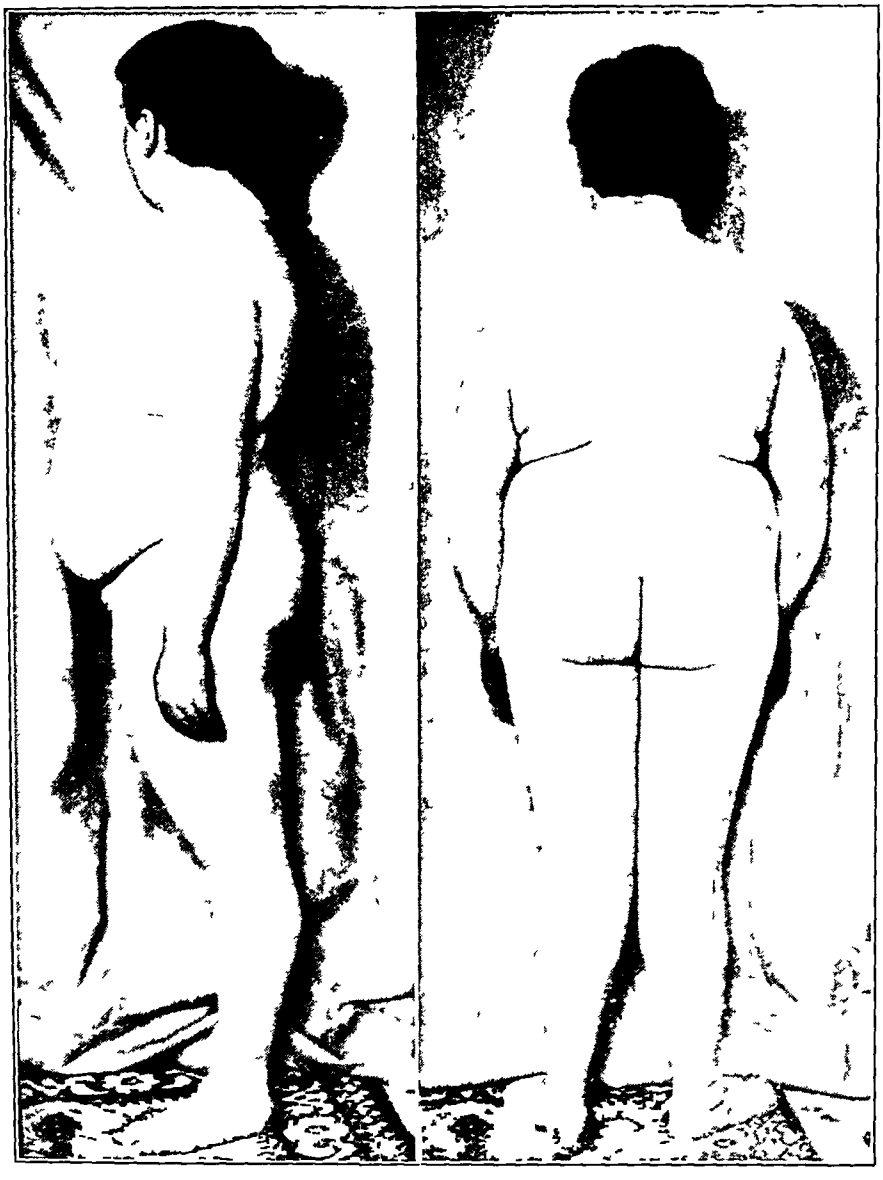

Fig 1—Lateral view of patient 1 Note the obesity, lumbar lordosis, small hands and feet

Fig 2—Posterior view of patient 1 Notice the genu valgum and the distribution of fat on the body

Examination—The patient presented the general appearance of a blind fat boy (Fig 1), height in stocking-feet 4 ft 9½ in, head fairly large supraorbital ridges not well developed, lower jaw rather small The teeth were crowded together on both jaws No marked disproportion existed between the length of the body and that of the extremities There was marked genu valgum (Fig 2) The hands were small and chubby, with delicate tapering fingers (Fig 4) The feet were also very small and there was flat-foot on both sides

The fat over the whole body was increased, the weight being 166½ pounds Deposits of fat were especially marked in the mammæ buttocks, abdomen

and above the symphysis pubis (Figs 1, 2, 3) These gave the figure a feminine appearance The penis was very small and almost covered by the mass of fat about the mons veneris The scrotum was small and buried in fat Both testicles were of infantile type, the left being descended normally, the right felt at the external ring

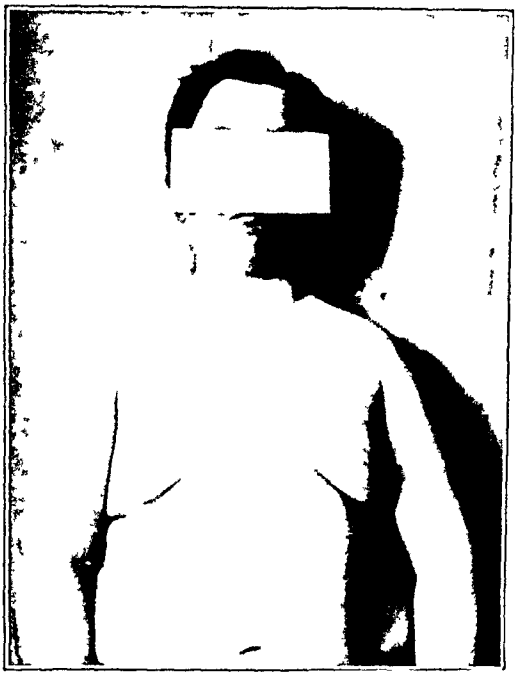

Fig 3—Anterior view of patient 1 Notice the distribution of fat

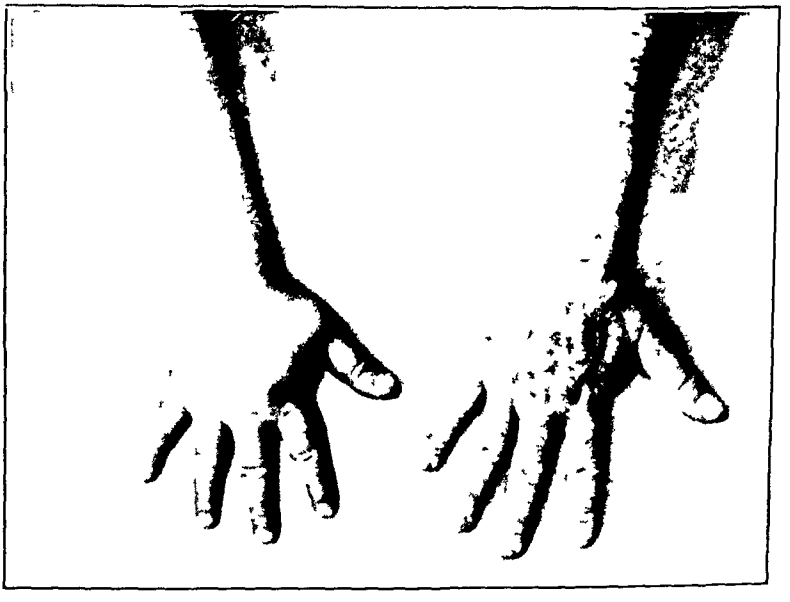

Fig 4—Hand of patient 1 (to the left)—Compared with hand taking a No 7 glove Note the small size, the tapering fingers and the delicate skin

The hair over the head was normal, over the body, it was very fine and soft No beard had ever developed and only a few coarse hairs were present in the axillæ and about the pubes The skin was soft and delicate The voice was high-pitched and of a melodious quality The patient presented many emotional

Fig 5 —Anterior view of patient, Case 2, by the side of a man 5 feet 8 inches high Note the adolescent figure and the absence of hair on the face and pubic region

Fig 6 —Patient 2 lateral view

characteristics of childhood, being affectionate, buoyant, but inclined at times to discouragement and weeping spells His general intelligence and intellectual development were good, and, in spite of his blindness, he was able to manage a small business very successfully

Since childhood the urine had always been increased in amount, at times according to the patient's statements, reaching eight or more quarts a day Repeated examinations of the urine showed a specific gravity which did not vary from 1,003 to 1,001 The urinary examinations were otherwise negative

The eyes were completely blind An examination showed "Both pupils slightly dilated, the left one more than the right Neither react to light, the light perception being *nil* Some nystagmus is present, probably due to inability to fix objects Extrinsic eye muscles normal Ophthalmologic examination shows clear media The fundus is somewhat over-pigmented, but probably not pathologically so Both nerve heads show clear margins and are bluish white in color The objective picture is that commonly seen in primary optic atrophy The vessels show no evidence of pressure"

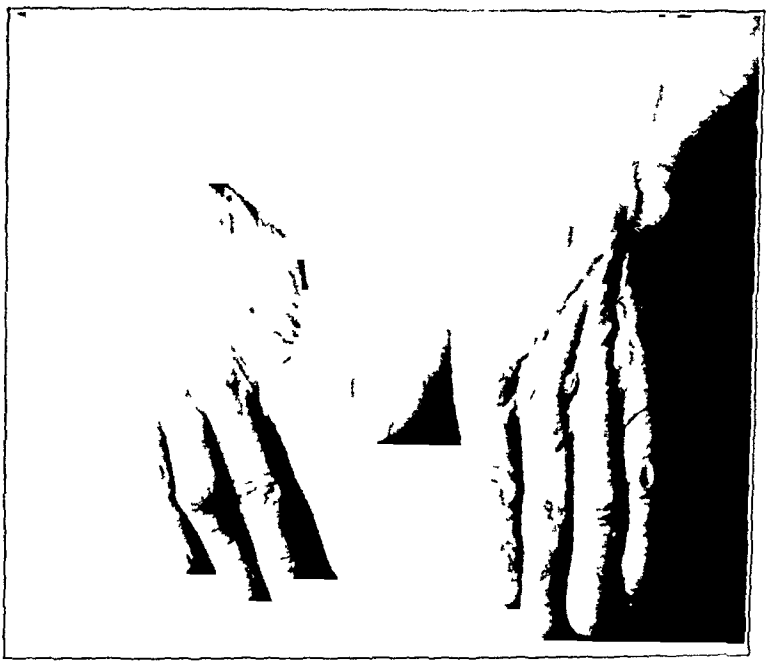

Fig 7.—Hands of patient, Case 2 Note the long slender fingers and dry skin

Two attempts were made to obtain radiographs of the skull but the plates were not good As the patient complained of headache after having been exposed to the *x* ray, no further efforts in this direction were made Plates of the hands showed complete fusion of the metacarpal and phalangeal epiphyses The lower epiphyses of the ulnar and radius were also fused but the lines of fusion were plainly visible and were indicated by notches on the edges of the radii so that the fusion was probably recent and considerably delayed beyond the normal[4]

The history of brain tumor, the stunted growth, optic atrophy, obesity, sexual infantilism and diabetes insipidus leave no doubt as to the presence of a tumor in or near the pituitary gland producing symptoms recently attributed to hypopituitarism The patient took the powdered

4 Rotch, T M, and Smith, H W A Study of the Development of the Epiphyses of the Hand and Wrist for the Purpose of Classifying the Cadets at Annapolis, Tr Assn Am Phys, 1910, xxv, 200

anterior lobe of the hypophysis, 15 gr (1 gm) a day, for over a month but without marked effect More recently he has been given the powdered thyroid glands, but after about two weeks he complained of pains in the head, dizziness and apprehensive sensations which led to a discontinuance of the medication

CASE 2.—*Since the age of 13, periodic headaches with vomiting Mild sexual infantilism Adolescent height and figure Bitemporal hemianopsia with primary optic atrophy Bony changes in the region of the sella turcica*

History.—A man, aged 40, first entered the University Hospital at Ann Arbor, July 7, 1910, complaining of dimness of vision, constipation, palpitation of the heart and general weakness His family history was negative, except that one sister was suffering from a nervous trouble Patient had had the ordinary diseases of childhood He denied venereal infection As a child he had gone to school and had had no difficulty in keeping up with his classes At about the age of 13 he began to suffer from periodic headaches which were usually associated with vomiting, coming on one or two hours after the onset of the

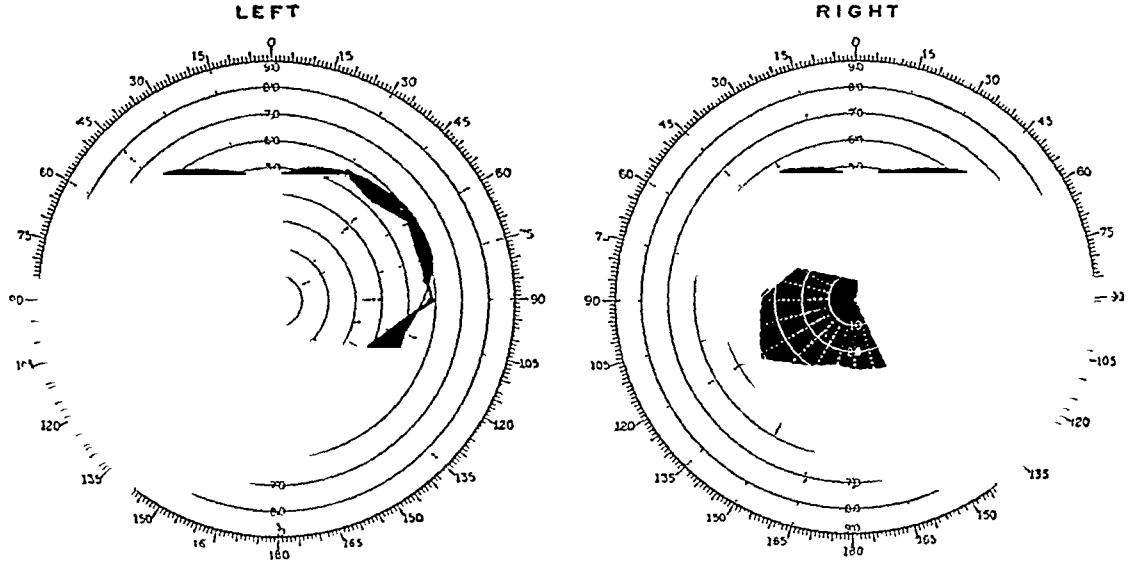

Fig 8.—Visual fields for candle light in second case showing the bitemporal hemianopsia

headaches These headaches often seemed to be precipitated by hard work, but they came at fairly regular intervals of one to two months His habits had been good, he had used alcohol rarely and had not used tobacco, tea, or coffee He had had occasional nocturnal emissions between the ages of 14 and 20, but none since then He had never married and had never had sexual intercourse

The present trouble, in his opinion, dated back three or four years During this time the headaches had increased greatly in severity, but the associated vomiting had lessened so that at the time of admission he rarely vomited The headaches usually centered about the frontal region, extending down over the eyes His sight began to fail about two years previously and the failure had gradually increased He had become constipated, nervous, and inclined to isolation Six years before he was advised to drink large quantities of water and he believed that in the last year he had been unusually thirsty The patient left the hospital July 13 but returned Nov 19, 1910, stating that his headaches had become more troublesome and that he had had some discomfort in the epigastrium without nausea or vomiting His sight had fluctuated considerably, but had become worse on the whole

Examination—Dec 2, 1910, the patient appeared to be a short, slender and delicately proportioned man with a figure resembling that of a male adolescent (Figs 5 and 6) Height in stocking feet was 5 feet 2 inches, weighed 76 pounds The head was well formed the thoracic spine showed a slight kyphosis, the hands (Fig 7) and feet were relatively long and slender The skin over the face and hands was sallow yellowish, dry and scaling, over the covered parts of the body it was soft and rather delicate The cheeks and lips showed a few thin, colorless hairs, the hair over the body was fine and colorless, and there was almost an entire absence of axillary and pubic hairs The penis appeared normal, the testicles were small and rather soft The patient seemed nervous and emotional The pupils were equal and reacted well to light and moderately well on accommodation there being no paralysis of the extra ocular muscles The vision was so diminished that the patient could hardly count fingers Ophthalmoscopic examination in the university eye clinic showed a primary

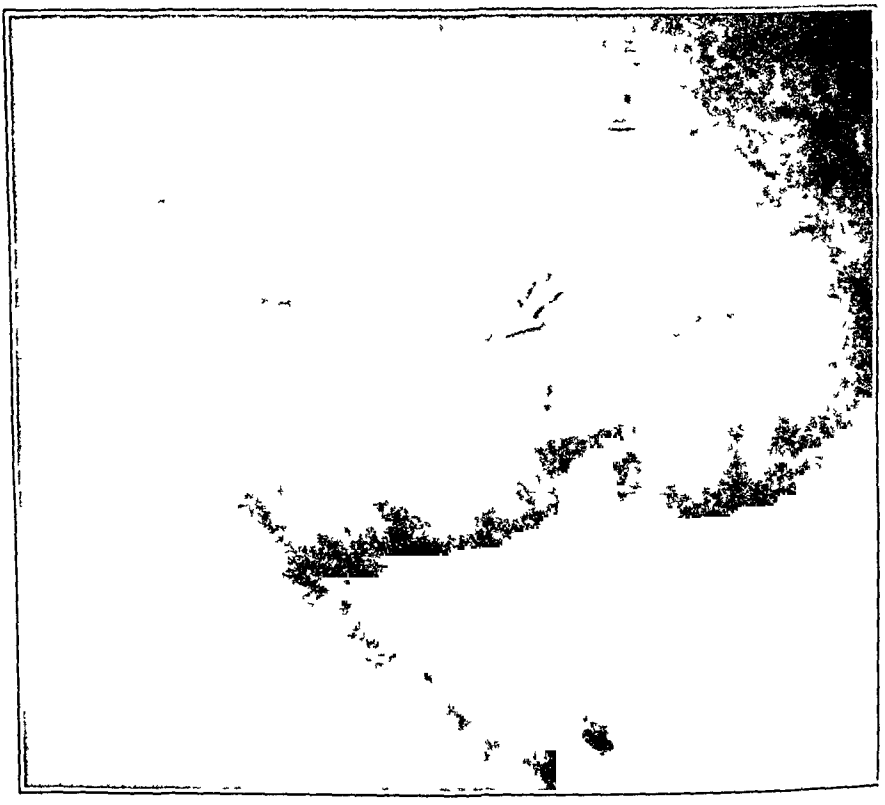

Fig 9—X-ray plate of the base of the skull, Case 2 showing absence of normal outlines of sella turcica The arrow points to the sella region and it is possible that the large pale area represents the abnormal sella (natural size)

optic atrophy The visual fields, as determined by a lighted candle, showed a bitemporal hemianopsia (Fig 8) The general strength was diminished but there was no definite paralysis and no disturbances of cutaneous sensation The tendon reflexes were everywhere active, the skin reflexes not increased The thyroid gland was neither seen nor felt Lungs, heart, and abdomen were negative A single blood-pressure determination on the first admission gave a systolic pressure of 110, but on the second admission it was taken repeatedly and was constantly low, ranging from 84 to 87 Wassermann reaction, gastric analyses, and microscopic stool examinations were negative The urine, of which 1 to 2 liters were passed daily, showed a constantly low specific gravity, the average of twelve examinations being 1,006, with 1,004 and 1,010 as extremes A restriction of liquids for a week did not raise the specific gravity Two

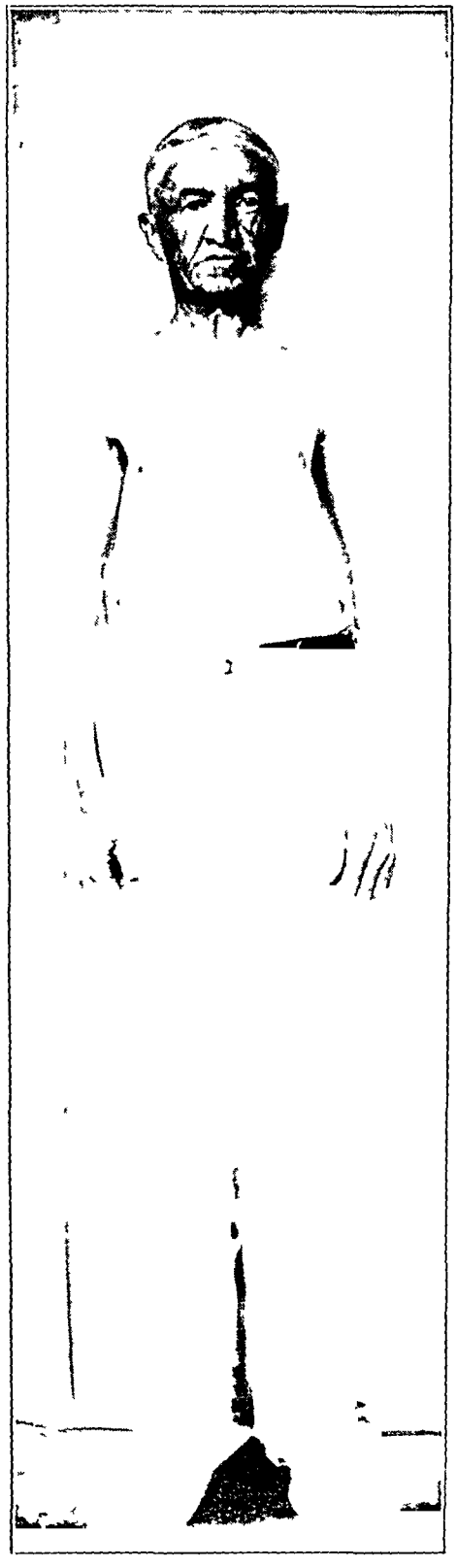

Fig. 10.—Anterior view of third patient showing small figure and wrinkled skin

radiographic plates (Fig 9) taken transversely across the head showed an absence of the shadows normally cast by the bones surrounding the sella turcica Plates of the hands wrists, elbows and knees showed completed fusion of the epiphyses The possibilities of operation were discussed with the patient but he declined on account of the danger and our inability to promise a restoration of sight

CASE 3.—*Retarded sexual development Small frame Large sella turcica*

History.—A man aged 52 came to the University Hospital at Ann Arbor April 24 1911 complaining of stomach trouble His family history was negative He had four brothers all of whom were of average height, ranging from 5 feet 7 inches to 5 feet 9 inches The patient had never been very robust Up to the age of 16 he had progressed normally in school but at that time he had an illness which was diagnosed as spinal meningitis and which interrupted his schooling His first definite sexual feelings and first seminal emissions occurred at about the age of 30 years This was followed by a period of masturbation and since then by subnormal sexual impulses The patient had never married and had never had sexual intercourse He had always had more or less indi

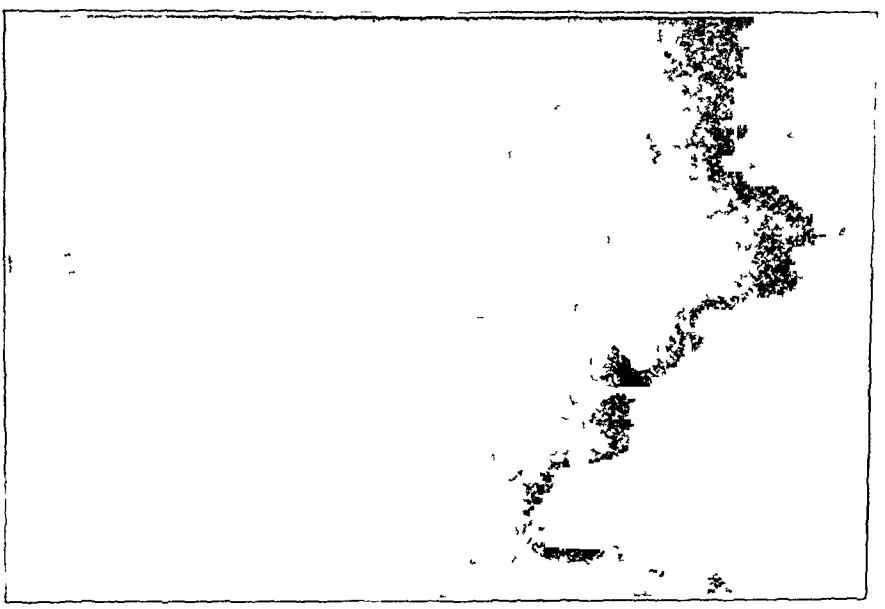

Fig 11.—Skull of third patient, showing, enlargement of the sella turcica cavity, with a wide entrance above (natural size) The arrow within the cavity points to the region of the tuberculum sellæ Ordinarily the shadow of the tubercle rises abruptly and joins that of the anterior clinoid process, giving a vertical shadow to the anterior wall of the cavity Here, however, the flattening of the tubercle gives a pointed appearance to the anterior end of the cavity The plate resembles that taken after death from the prepared skull of Erdheim's first patient but in my case the sella is larger and the flattening of the tubercle more pronounced (Erdheim J Ueber Hypophysenganggeschwulste und Hirncholesteatome Sitzungsb d k Akad Wissensch Math naturw Kl 1904 cxiii, Part 3, p 710)

gestion with intestinal disturbances He was in the hospital in 1906, at which time the diagnosis was made of neurasthenia, chronic gastritis, pigeon breast, and ulcerated septum He entered again on account of epigastric distress after meals, belching of gas, and irregularity of bowels Physical and laboratory examinations failed to show any definite organic cause for these complaints

Examination.—The patient was a short man, 5 feet 2½ inches in his stocking feet weight 91½ pounds without clothes (Fig 10) Like the preceding patient

he was delicately built, the bones were small and slender, the hands relatively long and slender The chest was rounded and was asymetrical, with a markedly protruding sternum There was slight kyphosis in the upper thoracic spine The skin of the face was deeply tanned and much wrinkled The hands were cyanotic The skin over the exposed parts of the body was dry and scaly, over the covered parts normal The growth of hair was normal, the external genitalia rather small, knee-jerks were active, Wassermann reaction negative The specific gravity of the urine was 1,012, quantity was not increased Examination of the eyes in the eye department of the University Hospital showed a slight general limitation of the visual fields due to cortical cataracts The optic nerves were rather pale, with arteriovenous compression A radiograph of the skull showed a sella turcica somewhat larger than normal and characterized especially by an absence of the shadow of the tuberculum sellæ, and by a wide entrance from above into the fossa (Fig 11)

We are indebted to the French school for numerous studies and discussions on the nature of infantilism Various definitions for the condition have been proposed Some would limit it to the persistence of childish or infantile characteristics in older people, while others prefer the more general conception of a "persistence in a given person of characteristics, bodily and mental, which belong to one of less advanced age' The Brissaud type of infantilism in which the characteristics of infancy or early childhood are especially retained is described as follows "Round chubby face, lips projecting and plump, small nose, smooth face, fine clear skin, fine hair, eyebrows and eyelashes scant, eyes prominent, large round cheeks, infantile face and head, skeleton under-developed, neck short and chubby, body long and cylindrical, abdomen prominent, limbs round and large, layer of fat over the whole body, infantile pelvis, lumbar lordosis, rudimentary sexual organs, no hair except on head, high-pitched voice thyroid small, mind slow, retardation of ossification, absence or retardation of second dentition" My first patient showed many points in common with this description of the Brissaud type of infantilism [5] In him development had been arrested early in life and he showed many of the bodily, mental and sexual characteristics of childhood Brissaud would attribute such arrested development to an insufficient thyroid secretion, but it seems certain that this conception is too restricted and that other causes may be operative So far as hypopituitarism is concerned it is possible, of course, that this may influence the thyroid secretion or that it may be secondary to a thyroid disease, for the two glands bear an intimate relation to each other According to Frankl-Hochwart, however, constant anatomic changes have not been demonstrated in the thyroids of patients with this type of pituitary disease, and the unusual intelligence of the first patient would speak against a marked thyroid insufficiency in his case

The bodily development of the second patient differed from that of the first chiefly in the absence of obesity and in the general appearance

5 Brissaud L infantilisme Mal Nouv iconog de la Salpêtrière 1907 xx

of adolescence rather than of childhood The infantilism in this case bore a general resemblance to that which usually goes under the name of the Lorain type, and has been described as follows "Small stature, delicately-formed, slender skeleton skin soft and pale, large shoulders, lower extremities long and slender, trunk relatively small, infantile sternum and pelvis epiphyses normally united, no fat, abdomen normal, finely chiseled face, voice high, neck long, genital atrophy absence of or slight secondary sexual characteristics" It has been claimed that these two types of infantilism are essentially different and that in the Brissaud, the fusion of the epiphyses is delayed, while in the Lorain type the fusion occurs at the normal time or prematurely The value of this criterion has been shaken by the fact that in some cases of the Lorain type epiphyseal fusion has been retarded [6] It would seem that the two are not essentially different but that in the Brissaud type development is arrested at an earlier stage than in the Lorain type, due either to an earlier onset or to a more severe causative agency

The Lorain type of infantilism appears to be rather unusual in pituitary disease, possibly on account of the frequent development of obesity which would mask its characteristic features However, in one of Levi's[6] patients and in that described by Lemann and Van Wart,[6] typical Lorain infantilism was associated with presumable disease of the pituitary gland It is important to note this occurrence because it serves to indicate that the same group of causes may give rise to the different types of infantilism Frankl-Hochwart believes that when pituitary disease occurs in early life obesity is more common than when it begins later, but this rule is subject to numerous exceptions In my second patient a mild type of hypopituitarism occurring just before adolescence was probably sufficient to stunt the growth and to retard sexual development without inducing obesity In the third patient the diagnosis is not well established, but the enlargement of the sella turcica and the general resemblance to the second patient suggest that we are dealing here with a mild form of hypopituitarism

The first patient showed a typical diabetes insipidus, with very large quantities of urine and a constantly low specific gravity Frankl-Hochwart found this condition mentioned in 7 per cent of the cases which he investigated On the other hand, diabetes mellitus was very rare in his series, much more so than among the collected cases of acromegaly

We are quite ignorant as to the precise nature of the diabetes insipidus which occurs in pituitary disease It has been shown that the posterior

6 Levi, E Contribution a l'etude de l'infantilisme de type Lorain, Nouv iconog de la Salpêtrière, 1908, xxi, 297 Lemann, Isaac I, and Van Wart, Roy M A Case of Infantilism with Absence of Thyroid and Tumor of Pituitary, The Archives Int Med, 1910 v, 519

and middle lobes of the gland may increase the flow of urine,[7] and it is possible that an overaction of this portion of the gland may be associated with a diminished activity of the anterior lobe Possibly, however, the diabetes insipidus results from nervous impulses excited by an irritation of structures at the base of the brain In my second case, the urine was not increased markedly in amount, varying between 1 and 2 liters per day during his stay in the hospital The examinations, however, were interesting in that they showed a constantly low specific gravity which averaged 1,006 and never exceeded 1,010 E Meyer[8] has shown that in true diabetes insipidus the kidney is unable to secrete concentrated urine, and I found that even though this patient took less than 500 c c of liquid per day, the specific gravity of his urine was not raised Unfortunately it was not possible to make an accurate metabolic study

CONCLUSIONS

1 The infantilism associated with disease in or near the pituitary gland may resemble either the Brissaud or the Lorain type of infantilism

2 A constantly low specific gravity of the urine in patients with such disease may be the equivalent of a mild diabetes insipidus

902 Baldwin Avenue

7 Schafer The Functions of the Pituitary Body, Proc Roy Soc Biol, lxxxi, 442

8 Meyer, E Ueber Diabetes insipidus und andere Polyurien, Deutsch Arch f klin Med, 1904, lxxxiii, 1

PERSISTENT PATENCY OF THE DUCTUS ARTERIOSUS BOTALLI IN THE DOG

CLYDE BROOKS
PITTSBURGH, PA.

This case is reported because it includes not only the ordinary clinical observations but also direct manometric blood-pressure and intratracheal respiratory pressure tracings together with autopsy findings with histological report all on a dog which had a widely patent ductus arteriosus Botalli with aneurysm of the duct itself and the beginning systemic and pulmonary aortæ. A further favorable condition was that death in this case was caused by rapid suffocation. By this means the physiological and pathological conditions or changes caused by the persistent patency of the ductus were all preserved unobscured by any other overshadowing diseased condition as is usual at autopsy.

From a study of the case from these different points of view it seems that the clinical symptoms and abnormalities in blood-pressure and respiration and the changes found in the various organs which were associated with the persistent ductus, are all related, and apparently constitute a condition as a whole which leads to a tolerably satisfactory conception of the nature and cause of the changes present.

The case reported here is that of a dog which was used for a demonstration in the Pharmacological Laboratory of the University of Pittsburgh. Following are some of the notes from the clinical description based on the examination preliminary to anesthetizing the animal.

NOTES ON CLINICAL EXAMINATION

March 15, 1910. 2 30 p. m. Adult well nourished male dog with yellow hair. Weight 14 000 gm. Behavior normal, rather quiet, not excited. Respiration 10 in ten seconds. (Owing to his looking about and inquisitively sniffing the air, some difficulty was experienced in making the observation.)

At 2 48 p. m. Pulse from the femoral artery 21 in ten seconds, somewhat irregular showing a periodic symmetrical arhythmia, which seems to bear a close relationship to the respiratory movements. Inspection showed a greatly exaggerated cardiac impulse, both as to force of impulse and as to area of surface involved in the movements of the heart beat, and also brought out clearly the periodic arhythmia which was observed in counting the pulse. In addition there was a powerful thrill. This thrill continued and swelled out strongly during systole and was less powerful though still very well marked, during diastole. Tentative diagnosis made at this time. Aneurysm with aortic regurgitation.

From the Laboratories of Physiology and Pharmacology of the University of Pittsburgh.

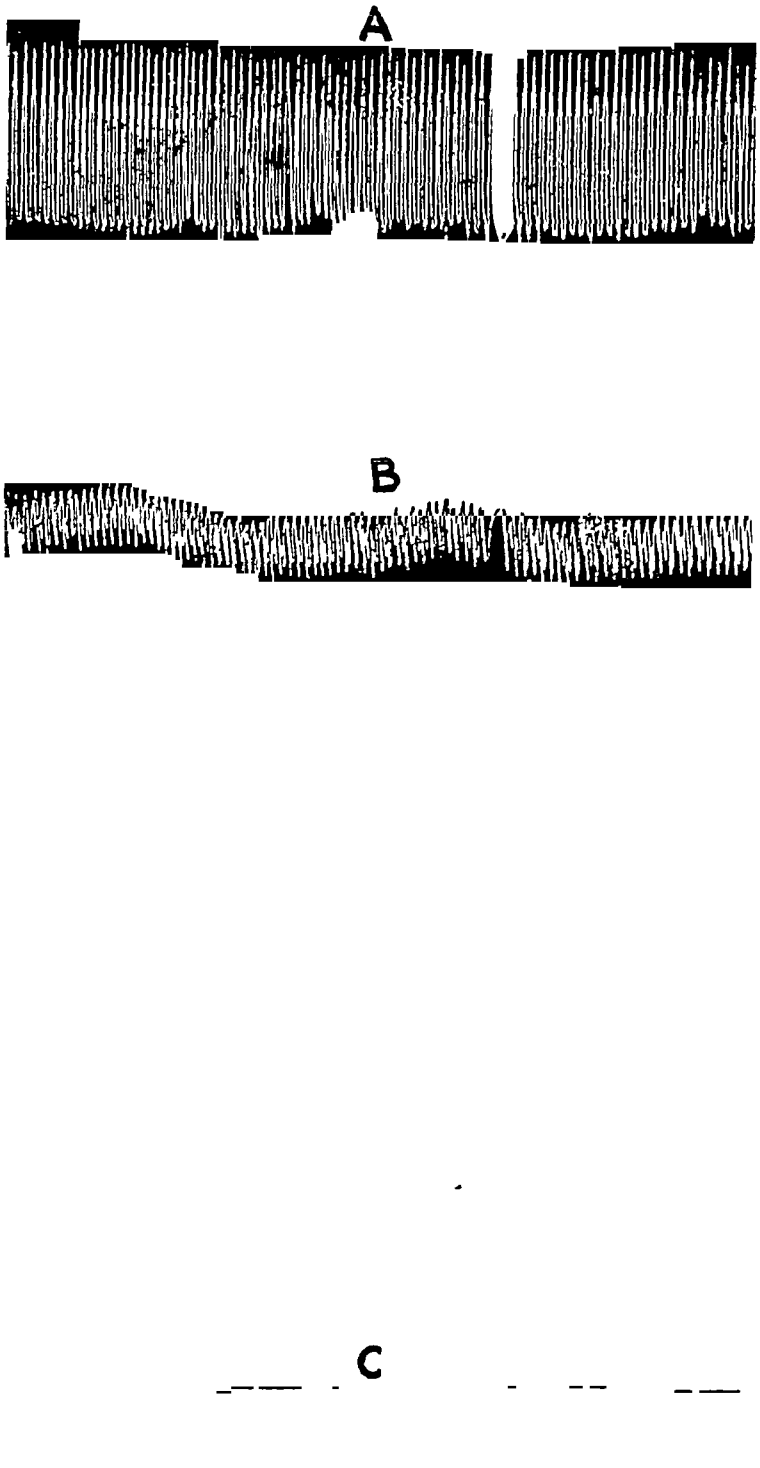

Fig 1.—Tracing showing simultaneous records of carotid blood-pressure and intratracheal respiratory pressure, taken from a dog which had a persistent patent duct of Botal. A, respiratory tracing (inspiration gives upstroke). B carotid blood-pressure tracing. C base line.

At 2 50 p m Pulse 21 in ten seconds Respiration 5 in ten seconds Pupils measured in the bright light 2 5 mm in diameter

Following are some of the notes made during the demonstration which show the results of anesthesia and blood-pressure and respiration observations They are sufficient to show the character of the pulse and respiration

NOTES ON BLOOD-PRESSURE AND RESPIRATION

2 51 p m Began the administration of ether Animal struggled
2 51 45 p m Animal relaxed but slightly and winked its eyes frequently
2 52 15 p m Pupils dilated Dog still winking
2 52 30 p m Pulse 33 in ten seconds Respiration 9 in ten seconds
2 53 p m Pupils dilated No reflex on touching the conjunctiva Intra orbital pressure considerably increased
2 54 p m Pulse 39 in ten seconds Respiration 12 in ten seconds
2 55 p m Animal not well relaxed Anesthetic increased
2 56 p m Animal sufficiently well relaxed Operation begun Tracheal cannula inserted, connected with the ether bottle and with a short side connection to a tambour which gave upstrokes on inspiration Three way cannula inserted into right common carotid artery and connected with a mercury manometer by a short rubber tube The ether was crowded to the maximum by shutting off entirely the air hole in the tracheal cannula and by shaking the ether bottle
3 00 p m Pulse 36 in ten seconds Respiration 15 in ten seconds Began blood pressure and respiratory tracings
3 01 30 p m Pulse 36 in ten seconds Respiration 12 in ten seconds
3 02 p m Pulse 32 in ten seconds Respiration 12 in ten seconds
3 02 30 p m Pulse 29 in ten seconds Respiration 15 in ten seconds

Remark.—Throughout these counts the pulse alternated in character First, one beat was very strong and trip hammer in character while the next one was very weak Occasionally there were complete notches or omissions

These observations are sufficient to give the main characters of the blood-pressure changes and respiratory movements and to show their relation to each other Measurements of the blood-pressure tracing taken by an ordinary mercury manometer (without maximal or minimal valves) show (Fig 1) a mean pressure of about 164 mm The minimal shown on the tracing is 156 mm and the maximal is about 172 mm The rate of respiratory movement is generally about one-half that of the pulse-rate During inspiration the blood-pressure falls, and during expiration it rises

Then follow observations of the action of magnesium sulphate on the animal and finally death which was caused by clamping the trachea

When the thorax was opened aneurysmal dilatation of the beginning systemic and pulmonary aortæ was observed but patency of the duct of Botal was not yet suspected

Following is a brief summary of the chief findings of the autopsy which was held about an hour after the death of the animal

NOTES ON AUTOPSY

March 15, 1910, 5 30 p m The body is that of a well nourished male dog with short yellow hair Length of body from tip of nose to root of tail, 55 cm Weight about 14 kilos Body slightly warm and not in rigor mortis except

slightly in the jaws and shoulders Pupils moderately dilated Sclera clear white Large recent open wound extending lengthwise from the thyroid cartilage to the diaphragm and opening the thorax all the way down in the mid-line Superficial lymph-glands not palpable No other external abnormalities The abdominal cavity shows no changes There is an abundance of fat present The kidneys are rather small and firm, their cut surface is pale, and shows the cortical markings distinctly The capsule strips readily, leaving a slightly

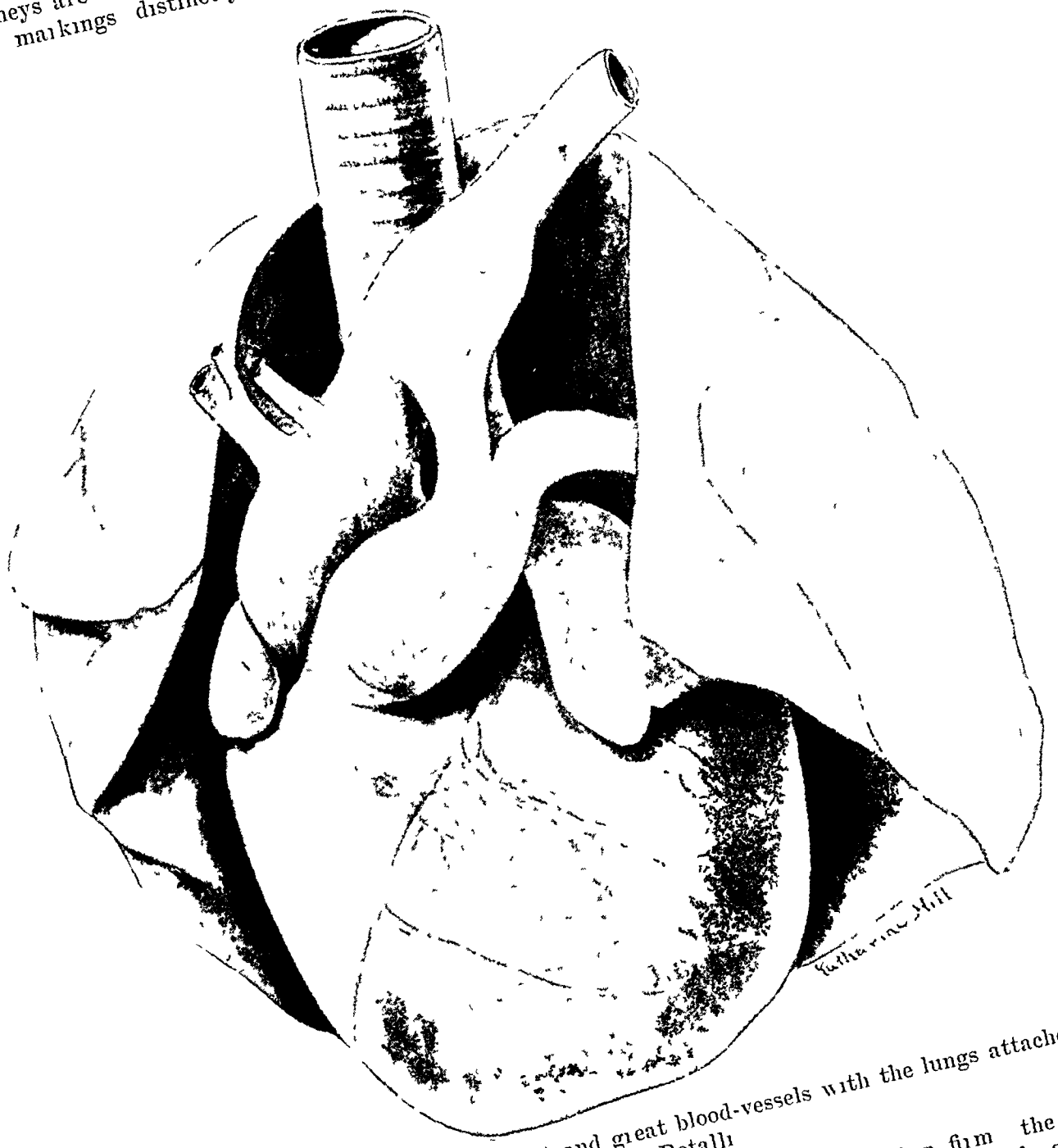

Fig 2—Drawing of the heart and great blood-vessels with the lungs attached showing the persistent ductus arteriosus Botalli

granular surface The liver is dark in color and feels rather firm the cut surface shows nothing abnormal The gall-bladder is distended with pale green bile Examination of other abdominal viscera shows no abnormalities Both lobes of the thyroid are small and poor in colloid The parathyroids are normal The lymph-glands in general are not enlarged The bronchial lymph-

glands are black but not swollen The heart and its accompanying large vessels and the lungs are removed *en masse* The lungs contain considerable black pigment They are slightly discolored, and show small areas of emphysema (due doubtless to positive artificial respiration) They feel slightly tough and leathery, and they do not collapse quite so readily as normally There are no areas of consolidation or cavities The cut surface shows that the branches of the pulmonary arteries stand open There are no other apparent abnormalities

The heart is very large broad and curiously blunt looking (Fig 2), resembling in shape a turtle's heart The apex is made up entirely of left ventricle The walls of the left ventricle are greatly thickened measuring 20 mm near the base A less thick area is palpated near the apex The walls of the right ventricle, which occupies only the upper and right side of the heart are also much thickened They measure at points near the base 5 to 6 mm Both auricles are also thickened The interventricular septum measures from 10 to 12 mm The cavity of the left ventricle is greatly enlarged The other cavities of the heart are about normal in size The foramen ovale is closed The auriculoventricular openings are normal in size Both aortic openings of the heart are also normal in size All the aortic and mitral and tricuspid valves are normal except that they appear stronger and heavier than normal This is especially true of the mitral leaflets The coronary arteries are thickened but show no patches The systemic and pulmonary aorta are laid open by a cut beginning from a point on the ventricles about 3 cm below the mouth of the coronary artery and extending upward to a point far enough to expose the mouths of thirteen intercostal arteries inside the aorta The circumference of the aortic orifice when laid open measures 4 5 cm, that of the pulmonary 4 2 cm The beginning aorta just above the aortic orifice forms a large bulbous dilatation The intima in this region is smooth but the vessel wall is of a diffuse slightly yellowish color At the widest part the vessel laid open measures 5 8 cm There is a similar bulbous dilatation at the beginning pulmonary aorta, with similar yellowish coloration of the walls but with glistening intima This dilatation is not so large as that of the systemic aorta It measures laid open, 5 4 cm in the widest part At a point just opposite the region where the arterial ligament normally comes off from the systemic aorta there is a second widening of its lumen into an oval bulbous dilatation This bulb is smaller than either of the other two Its wall measures 5 cm in width when laid open There is no narrowing of the aorta beyond the region of the ductus The intima is smooth and glistening The vessel wall has a slightly yellowish color Coming off from this dilatation and connecting it with the pulmonary aorta is the widely patent duct of Botal (Fig 2) This duct is itself widely dilated at the aortic end and narrows gradually till just at the pulmonary opening where it narrows abruptly The duct is therefore funnel shaped with the wide end opening into the aorta and the narrow end opening into the pulmonary aorta Its aortic opening is about 14 mm in diameter (It cannot accurately be determined, for it merges at the distal side into the wall of the aorta without any line of demarcation) Laid open it measures 43 mm The pulmonary opening forms a smooth elevated ring apparently composed of thickened intima This ring is surrounded by an elevation which appears to form a nozzle like ostium The pulmonary opening which is almost a perfect circle, is 4 5 to 5 mm in diameter The length of the duct itself is about 20 mm The whole effect is that the duct itself forms a rather bulbous, pouch like, funnel shaped tube which originates from the aorta with a very wide mouth, almost as wide as the normal aorta itself, and opens into the pulmonary aorta with a much smaller mouth The effect of the opening at the aorta is to leave at the proximal (nearest the heart) margin a sharp edge in the blood stream The pulmonary opening is almost half the diameter of the normal pulmonary aorta itself This patent duct of Botal is connected at an angle of about 40 degrees with the systemic and pulmonary aortæ

After the autopsy and before placing the specimen in preserving fluid the continuity of the heart and great vessels and ductus arteriosus was restored by

suturing with fine silk I wish at this point to thank Prof C C Guthrie for the accomplishment of this task I then made the drawing which is intended to give an impression of the appearance of the heart and great vessels with lungs attached, all parts being made true to scale as measured at this time The drawing which is published here (Fig 2) is a copy made later from this measured drawing, together with the preserved specimen

HISTOLOGICAL REPORT

Tissues were fixed in Zenker's fluid, embedded in celloidin, and stained with hematoxylin and eosin, and also with orcin The histological findings are remarkable principally on account of the absence of many marked abnormalities which might have been suspected

The heart showed nothing abnormal The branches of the pulmonary were large and heavy walled, but showed no inequalities in the thickness of the different layers in different arcs of the circumference nor any patches nor fatty changes The elastic tissue was normal in amount and appearance In many areas the lungs showed thick-walled alveoli The blood vessels were prominent and the capillaries were over-filled with blood The capillaries in places bulged out into the lumen of the alveoli, forming bud-like projections The lungs contained a large amount of pigment as is usual in dogs in Pittsburgh Elastic tissue was present in fully the normal amount There were no *Herzfehlerzellen* or other evidence of chronic passive congestion of the lungs Scattered throughout the section were many areas showing enlarged nodular masses of plain muscle surrounding the bronchioles There was an exudation in the bronchi, and some areas of emphysema and atelectasis

The spleen showed a large proportion of trabecular tissue with the Malpighian bodies irregular in size and distribution The blood-vessels of the spleen were somewhat sclerotic There were also cells bearing golden-brown pigment The capsule was wrinkled The portal branches in the liver were distended The blood capillaries were well filled, but not to the point of congestion The liver-cells were normal except for very slight fatty changes

The kidneys were normal except for a slight increase in interstitial connective tissue

The lungs were in very good condition except the exudate into the bronchi and the patches of emphysema, which were no doubt due to the long-continued positive artificial respiration, and also except some thickening of the branches of the pulmonary arteries, and areas of bud-like dilatation of the capillaries, together with many enlarged nodules of plain muscle surrounding the terminal bronchioles and with some thickening of the alveolar walls

There was chronic passive congestion of the spleen which had previously been greater than it was at the time of autopsy

DISCUSSION OF LITERATURE

Previous to the recent complete review of the literature and discussion of the present status of our knowledge of the whole subject by H. Gideon Wells,[1] there was no adequate treatment of this matter in English, but his article renders unnecessary any extensive review or discussion of literature at this time

Also there is a splendid article by Goodman[2] dealing especially with the symptoms and physical signs, and containing a bibliography

1 Wells, H Gideon Persistent Patency of the Ductus Arteriosus Botalli, Am Jour Med Sc, 1908 (136), 381

2 Goodman, Edward H Report of a Case of Patent Ductus Arteriosus Botalli, with a Study of the Cases Heretofore Published. Univ of Penn Med Bull Phila, 1910, xxiii 509

The occurrence of simple primary patency of the ductus arteriosus Botalli in man is very rare, especially if simple primary patency is understood to include only those cases in which the ductus is open for the transmission of blood without any other overshadowing congenital abnormality, such as stenosis of the pulmonary aorta Wells reports in the entire literature only forty-one cases, in only twenty of which the patients reached adult life I have found in the literature at my command, one instance of the condition in the dog [4] In aquatic mammals the ductus arteriosus normally remains patent for some time after birth but an open canal in the adult is regarded as pathologic For example, persistent patency has been observed in the seal [3]

As Wells points out with reference to man so is it with laboratory animals, that if careful systematic search were made at autopsy, more instances would undoubtedly be found

It is probable that in simple primary patency, such a widely patent ductus arteriosus as the one under observation occurs only extremely rarely

Liénaux[4] observed a case of persistence of the duct of Botal in a little dog 5 or 6 months of age, brought to him for treatment because it was weak and refused food The little dog showed a frequent cough with no expectoration, rapid respiration with audible rough sound There was an increased dulness over the region of the heart Palpation gave a *frémitus cataire,* or a thrill resembling the purring of a cat, which was marked both on the right and the left sides There was a murmur which was of maximal intensity over the anterior part of the heart The femoral pulse was strong The jugular pulse was marked, and coincided with the ventricular systole Temperature 40 1 C The dog died two days later

The autopsy showed the left ventricle much enlarged and thickened The pulmonary orifice was insufficient to the water test The total volume of the heart was much increased The duct of Botal was patent and was about the size of the pulmonary aorta, and the walls of the patent duct were thicker and more rigid than those of the pulmonary aorta The beginning systemic aorta was enlarged as far up as the place where the duct of Botal branched off This aneurysmal part had thin rigid walls The trachea was compressed by the aneurysm, which accounts for the rough breathing

Dr Kate Campbell Mead[5] has reported a case of persistent patency of the duct of Botal in an adult woman Although the patient had been

3 Jammes and Mandoul Sur la persistance du canal artériel chez le phoque, Bull de la Soc d'hist nat de Toulouse, 1905, xxxviii, 3

4 Liénaux, E Un cas de persistance du canal artériel chez le chien, Ann de méd vét, 1898, xlvii, 416

5 Mead, Kate Campbell Persistent Patency of the Ductus Arteriosus, Jour Am Med Assn, 1910, lv, 2205

troubled with heart symptoms since childhood, she reached adult life and married and went through pregnancy in very fair condition

Thayer's examination of the patient showed a long machinery murmur over the right ventricle with systolic accentuation, and with accentuation of the second pulmonic The loudness of the murmur high up suggested to him persistent patency of the duct of Botal Later the patient showed more aggravated circulatory symptoms with laryngeal cough, edema, meteorism, and scanty urine — leading to coma, and finally very suddenly to death

Autopsy showed the heart ruptured in three places in the right ventricle, with sclerosis of the coronaries and fatty degeneration of the myocardium The heart was greatly enlarged, especially in the right ventricle The heart weighed 395 gm (Normal about 250 gm) All cavities of the heart were enlarged and the walls thickened The walls of the right ventricle especially were thickened, being almost as thick as those of the left ventricle which were also thicker than normal The duct of Botal was patent It was funnel shaped with the large end 1 cm in width opening into the systemic aorta, and the small end about 4 mm in diameter opening into the pulmonary aorta, and forming a ring-like ostium of the thickened intima of the pulmonary aorta

In this case it seems that the persistent patency of the duct of Botal brought on a higher pressure in the pulmonary artery, which eventually led to hypertrophy of the right ventricle with sclerosis of the coronaries of that part of the heart This condition finally led to fatty degeneration which resulted in weakening of the myocardium and rupture of the heart, which was the immediate cause of death of the patient

DISCUSSION OF THE PRESENT CASE

Although there was a profound alteration in the circulatory apparatus in the dog concerned in this report, yet there was no change in the health or general well-being The dog was in fine health and vigor, and well nourished There was no blueness of the mucous membranes There was a heightened blood-pressure with arhythmia of the cardiac beat Another noticeable change of the circulation was the relation of respiratory movements to blood-pressure change [6]

6 It is to be remembered that normally in the dog the blood-pressure rises during inspiration and falls during expiration, except the change is slightly later than the change in respiratory movement, that is, the blood-pressure continues to rise for a short time after inspiration has ceased, and it continues to fall for a short time after expiration has ceased It is known that this relationship between blood-pressure and respiratory movements is not the same in all species of animals nor even in the same species under all conditions, for it is a very complex relationship which is dependent on several factors which vary with the rapidity, depth of respiratory movements, size of animal, and with the preponderance of costal or abdominal respiration Lewis Thomas Further Advances in Physiology, N Y 1909 p 144

In this dog the usual condition was reversed Inspiration was synchronous with a fall while expiration was synchronous with a rise in blood-pressure The explanation of this is probably that during inspiration while the lungs expanded, the blood from the aorta poured over into them This drain on the aorta caused a fall in blood-pressure Then during expiration the volume of the blood-vessels of the lungs was decreased so that the blood was squeezed out of them This would leave the pulmonary circuit filled so that less blood could escape across from the aorta through the ductus arteriosus into the pulmonary aorta Because the drain on the aorta was diminished, the blood-pressure would naturally rise in the systemic circuit Also it is probable that during inspiration as the lungs were expanding less blood was thrown out of them into the left auricle This would lessen the amount thrown out into the aorta and during expiration the compression of the lungs would discharge a larger volume of blood into the left auricle which would be immediately cast out into the aorta and would raise the blood-pressure It acted, according to this conception, as the establishment of a short circuit in the aorta during inspiration and with an interruption of the short circuit during expiration

The abrupt changes of pressure on the heart coupled with the abrupt changes in the volume of blood coming to the heart are probably associated with the arhythmia of pulse The sudden fall in pressure in the aorta at the same time with a sudden decrease in the amount of blood coming into the heart from the lungs would be sufficient to account for the omission of beats which was noticed above

The mixing of artificial and venous blood here must have been very considerable, but was not such as to cause marked blueness of the mucosa Of course blueness of the skin is not so easily recognized in the dog as in man But blueness would not be expected in this case, because the mixing, in all probability, consisted only in adding aortic arterial blood to venous blood of the pulmonary artery, and not *vice versa,* for the minimum aortic pressure recorded in our tracings never closely approached that of normal pulmonary arterial pressure Direct measurements of the pulmonary arterial blood-pressure were not made in this case, but judging by the records obtained from the carotid which may be considered as giving an index of the systemic aortic pressure, and also by the comparative size of the two ventricles, and since the ventricles appeared to beat synchronously, there is no evidence that the right intraventricular pressure ever overtopped that of the left

The high blood-pressure of this dog is not necessarily a matter for great wonderment, for it is not uncommon to find in lusty, vigorous dogs under an anesthetic a blood-pressure considerably above the average, furthermore, it is well known that the vascular mechanism is endowed

with great powers of compensation, and yet the pressure recorded is somewhat higher than the average observed under such conditions of anesthesia However, high blood-pressure is often associated with persistent patency of the duct of Botal, especially where compensation has occurred

The principal feature of pathological interest in this case is the patent duct of Botal, and scarcely less important are the changes in the organs found associated with this persistent patency First of these may be mentioned the bulbous dilatation of the beginning aortæ and the duct itself These dilatations may have been caused by the impact of the rebound of the column of blood brought about by the sharp changes in blood-pressure The stretching may also have been favored by the heightening of the general blood-pressure As to the presence of sclerosis in the vessels it may be said that there are no very profound changes The arteries appear slightly thickened and stand open when cut, and even show slightly yellowish color in the aneurysmal parts, but there is no atheroma nor roughness of the intimal surfaces Microscopically they show some thickening of the walls, but no irregularities in thickness in the different parts of the circumference

The curiously blunted turtle-heart form of this heart was apparently due to compensatory changes The heart as a whole was considerably larger and heavier than the normal This hypertrophy was enormous in the left ventricle The left ventricle occupied the whole of the apex and extended far up on the right side of the heart The right ventricle also was hypertrophied The walls of both ventricles were thickened, but the cavities were about normal in size This peculiar turtle-heart form was apparently due to the compensatory hypertrophy in response to the increased work thrown on the left ventricle, for in addition to its own natural work, it had to pump a large amount of blood through the lungs This in turn tended to heighten the pressure in the pulmonary artery which would offer increased resistance to the emptying of the right ventricle, and in that way would induce hypertrophy of that ventricle All the blood which was short-circuited from the aorta to the pulmonary artery would come back to the left side of the heart and have to pass again through the left auricle This additional work is sufficient to account for the hypertrophy of this part of the heart The increased resistance to the emptying of the right ventricle offered by the high pressure in the pulmonary artery could well be the cause of more or less damming back of blood into the right auricle such as might cause compensatory hypertrophy of this part of the heart Owing to this, all four chambers of the heart were put to additional work, which resulted in compensatory hypertrophy, which was most marked in the left ventricle where the additional work was heaviest

The whole pathological condition of this animal is that of a widely patent duct of Botal which acted as a short circuit in the aortic circulation, but which was so well compensated that there resulted no serious impairment of the general health or comfort of the animal This agrees with the findings of others on man that the prognosis in persistent patency of the duct of Botal is good Therefore an effort should always be made to differentiate between aneurysm and patent duct of Botal on account of the difference in prognosis From our experience with this animal it would seem that when necessary to administer an anesthetic to a patient with compensated patent duct, there need be no extraordinary precautions, for this dog showed even more than usual resistance to the effects of ether

VARIATIONS IN THE CONCENTRATION OF THE BLOOD AS AFFECTING THE OPSONIC INDEX

WITH A CRITICISM OF THE TECHNIC FROM THE PHYSICO-CHEMICAL STANDPOINT [*]

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It is now quite generally recognized that certain substances when dissolved in a solution in which leukocytes are suspended, markedly affect the ability of these cells to phagocyte The action of some of these compounds on phagocytosis is accelerative, thus, for example, the current notion of opsonic effect has for its foundation the idea that the bacteria present in conjunction with the leukocytes become sensitized or in some way altered so that the white cells may more readily engulf them Even though we grant the correctness of this claim of Wright and Douglas,[1] that the opsonins act specifically on the bacteria and not on the leukocytes, the exact explanation of the mechanism of the process has never been forthcoming There are, however, many facts which indicate that the phagocytic power of the leukocytes on inert suspensions, such as charcoal, dead bacteria, etc, can be markedly influenced in various ways It seems somewhat questionable whether the altered conditions affect the suspensions alone, a more reasonable deduction drawn from physical laws would indicate the effect as acting on the whole system of leukocytes, solution and suspension Without attempting a general discussion of this fundamental phenomenon from the physical standpoint, suffice it to call to mind the interesting experiments of Rhumbler,[2] which pointed to the probability that unicellular animals such as the ameba — morphologically similar to the leukocytes — perform most of their apparently vital functions merely as the result of surface-tension phenomena, and that many of these so-called vital movements can be duplicated with considerable accuracy with inert or inanimate substances

On the other hand, many facts have been accumulated to prove that phagocytosis can be altered quite considerably by changed environment as the result of certain substances present in solutions in which the leukocytes are suspended Thus, Hamburger and Hekma[3] in a series of

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[*] This work was carried out at the Bender Hygienic Laboratory, Albany N Y under a grant from the American Medical Association

1 Wright and Douglas Proc Roy Soc 1903 lxxii, 357, 1904 lxxiii 128

2 Rhumbler Arch f Entwicklungsmech 1898 vii 103

3 Hamburger and Hekma Biochem Ztschr, 1907 vii 102, 1908, ix, 275 and 512

papers, have presented a number of experiments which show quite conclusively that the character and composition of the medium in which the leukocytes are suspended, markedly influence the number of phagocyting white cells Changes in osmotic pressure and surface tension of the menstruum, brought about by altering the sodium chlorid concentration, cause the leukocytes to become much less prone to take up bacteria Thus, an increase in sodium chlorid concentration of the serum from 0 9 per cent to 1 0 per cent decreases the percentage of phagocyting cells from 34 6 to 11 84 per cent A decrease in the osmotic tension of the serum brings about like depressive changes If the concentration is not altered too considerably, the leukocytes regain their phagocytic power when the original osmotic tension is restored Too great alterations cause a lasting inhibition of phagocytic power Apparently there exists an optimum point at which phagocytic power is maximum, the normal osmotic concentration of the blood supplies this most favorable condition, variations in either direction from the optimum points result in a decrease in ability of the cells to take up bacteria or suspensions

Various investigators have considered the question of the effect of quinin hydrochlorid on phagocytosis When the substance is given internally or added to the serum *in vitro*, the effect is distinctly inhibitory In Hamburger and Hekma's work, the result was a decrease in the number of phagocytic cells After the administration of 1 gm of quinin, this substance must be contained in the blood in amounts approximating 0 01 per cent , while 0 001 per cent *in vitro* suffices to decrease the phagocytosis Manwaring and Ruh [4] working with the same substance found a slight increase in phagocytosis at 0 005 per cent , but with increased concentration, a decrease occurred Hamburger and Hekma[3] tested other substances such as hemoglobin and urea up to 2 per cent strength with negative results Sodium citrate in a concentration of 1 part to 27 parts solution was markedly deleterious Manwaring and Ruh[4] also tried the effect of certain antiseptics, their results pointed to a slight beneficial effect at low percentages for mercuric chlorid (1/120) and boric acid (1½), but with higher concentration inhibition of phagocytosis occurred

When one examines the immense literature covering all phases of the opsonic theory, it appears remarkable how little experimental work has been done to elucidate with scientific accuracy, from the chemical and physical standpoints, the exact mechanism of the supposed opsonizing power which substances in the blood exert on the bacteria On an insufficient foundation of facts has been built a superstructure of experimental work which is enormous and has covered almost all branches of clinical medicine It could only be expected, therefore, that it soon became clear that the application of the technic for the determination of the opsonic

4 Manwaring and Ruh Journ Exper Med , 1907, ix, 473

index as elucidated by Wright, even in the hands of skilled manipulators, gave results which were far from satisfactory and not in complete conformity to the claims of the discoverer The normal variations in the opsonic index indicated such great variations that only in certain specific infections can it be employed as an index of increased phagocytic power as the result of vaccine therapy

From the physico-chemical standpoint, apparently few attempts have been made to reach the cause for the wide variations in the opsonic index of normal persons All energy has been directed toward perfecting the bacteriological technic in the hope that such variations were the result of faulty manipulations, although it has long been noticed that certain general conditions of the patients, such as the amount of exercise must be held constant in order that the index might not show too great control variations

A few of the facts outlined above seem to indicate that other factors besides those of the presence of opsonizing substances (opsonins) influence to as great, if not to a greater, degree the ability of the white cells to engulf bacteria

In the attempt to determine some of these factors concerned in the variability of the opsonic index, the following experiments were conducted It seemed plausible, if not probable, that a portion of the so-called normal variations in the opsonic index might be ascribed to simple and normal changes in the physical character of the blood In order to elucidate this point, normal dogs were kept under constant conditions of diet, temperature, etc , the specific gravity, molecular and ionic concentration, electrolytic conductivity and viscosity of their blood were determined daily and compared with the opsonic index and with the red and white blood (total and differential) counts

DESCRIPTION OF THE METHOD AND APPARATUS

1 The specific gravity was determined by the pyknometer

2 The depression of the freezing point[5] was carried out by means of the usual Beckmann thermometer arranged for use with gaseous CO_2 as a freezing mixture according to the accompanying diagram (Fig 1) The main thermometer was held in a wide test-tube by a cork, on the side of which against the glass was cut a V shaped slit to allow the passage of a heavy platinum wire, the lower end of this was bent in shape to encircle the bulb of the thermometer The blood on which the determination was to be made was placed in this test-tube in quantities sufficient to cover the bulb of the thermometer and the fluid kept well in motion by the up and-down movement of the platinum stirrer This was accomplished by attaching the wire to a peg on a wheel revolved by a water motor The test tube containing the blood was inserted by a cork into a larger test-tube serving as an air-chamber In this cork a hole was bored to carry a thermometer reading from +40 to —20° C The larger test-tube was in turn inserted into a large cork paraffined into the base of a bottle, the bottom of which had been removed for the purpose The neck of this bottle inverted was placed on the freezing microtome

5 The depression of the freezing point will be referred to by the letter Δ

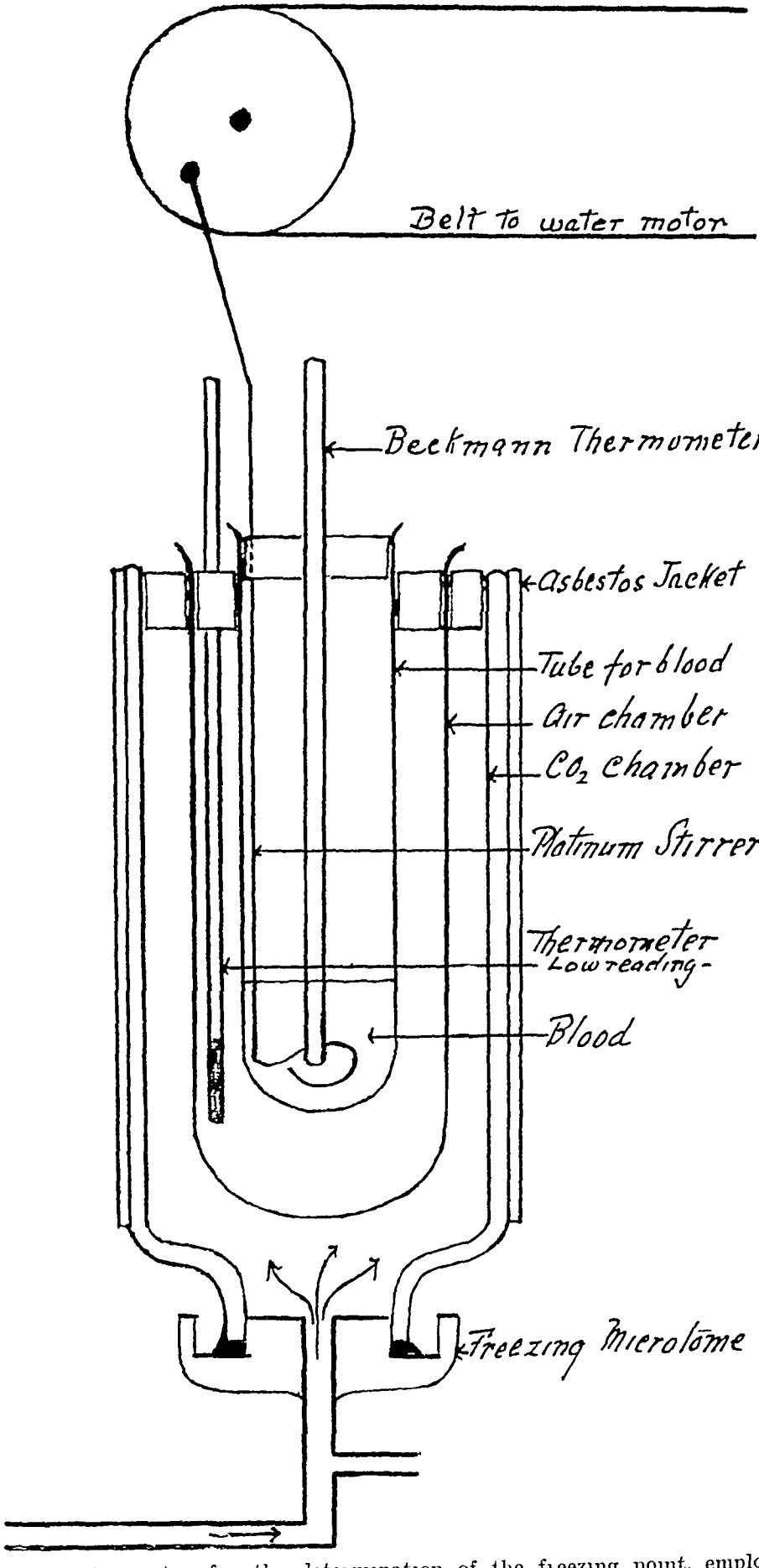

Fig 1.—Apparatus for the determination of the freezing point, employing carbon dioxid gas

3 Sedimentation was prevented by fastening above the bulb of the thermometer, in the viscosimeter proper, a circular wooden plate with a hole in the center, through which passed the thermometer This plate carried four metal wings projecting downward about the bulb and whose flat sides were radial to the long axis of the bulb and hence to the viscosimeter tube By the rotation of the thermometer around its long axis a thorough agitation of the blood could be brought about and sedimentation thereby prevented

4 Since the same capillary tube was employed in all determinations, the length and diameter factors in the determinations remained constant

5 The time during which a certain amount of blood passed through the capillary, was measured as follows A metronome (Label 8) was placed in a circuit with a double time marker the upper lever marking one third seconds on a revolving drum Three small glass tubes—one the bottle of a 10 c c pyknometer—were set in holes centered to the capillary of the viscosimeter which projected at (Label 10) about 1 mm through the rubber stopper in the neck of the bell jar these

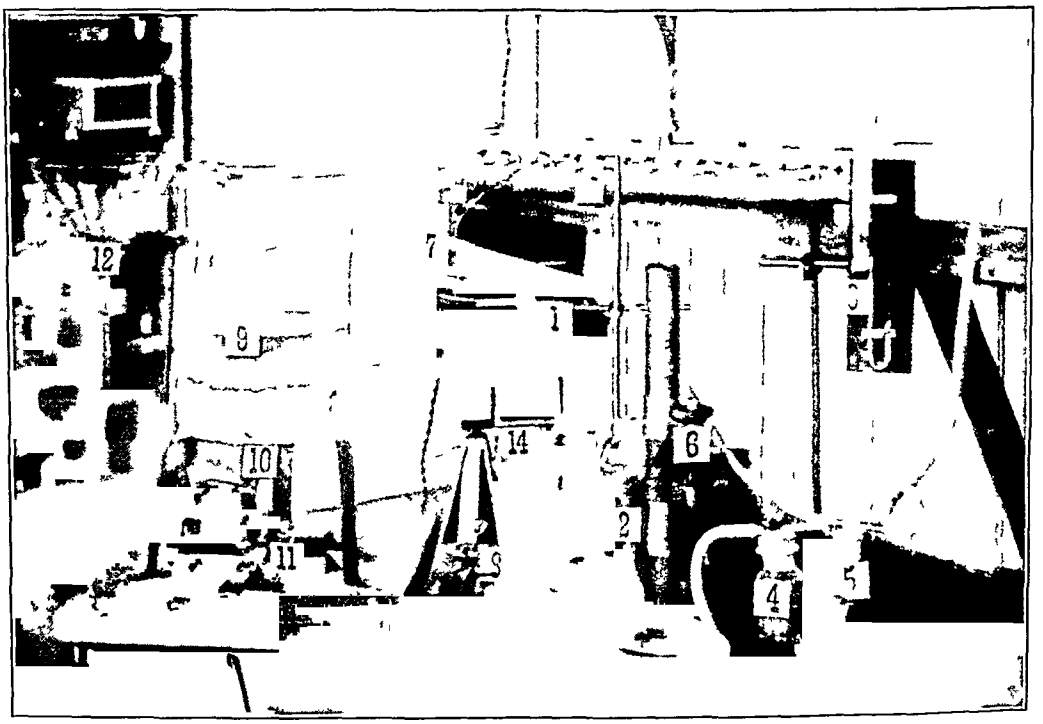

Fig 2—Viscosimeter

holes were bored out of a piece of wood movable from right to left or vice versa in a track This piece of wood carrying the bottles could be moved by a wooden handle pivoted as seen just to the left of Label 11 Each end of the sliding wooden carrier was provided with copper binding posts which made connection with similar posts at either end of the track Wires led to the battery from these binding posts, completed a circuit when the wooden carrier was moved to the end of the track in either direction In this double circuit was placed the lower time marker in such a way that when the wooden carrier was shoved either completely to the right or to the left, the time of connection was indicated on the drum When the carrier was at either end of the track, the capillary tube was centered over the right or left bottle The center tube served as a reservoir for the drops of blood leaving the capillary before or after the use of the apparatus The two outer small glass tubes were tared before being placed in the carrier

The procedure for making the duplicate determinations was as follows The level of the water having been lowered to below the top of the viscosimeter proper the stopper was removed The defibrinated blood at a temperature of 39 C was

strained through gauze into the viscosimeter which had previously been rinsed with the blood The stopper was replaced tightly and the level of the water in the bath raised above it By means of the wings on the thermometer the blood was stirred until the temperature of the bath and of the blood both became constant at 37 C After some practice, this could be brought about in a few minutes With the stop cocks closed, the pressure was then raised to 120 mm Hg by the mechanism of the two flasks (2 and 4) as described above The metronome and drum were started, and after some 10 or 15 drops had fallen into the center bottle the carrier was quickly shoved to the right, connection being made and registered on the drum at the exact instant that the first drop fell into the weighing bottle The blood dropped rapidly but not in a stream The only possible error in manipulative procedure occurred at this point[7]

At the end of the determinations the carrier was quickly moved so that the blood dropped into the center drip-bottle, connection was then broken and indicated on the drum The carrier was then shoved in the opposite direction to the left, bringing the other bottle under the capillary and registering the time on the drum The duplicate determination was completed as above At this time the lower tracing on the drum indicated the points when the first and the last drop had entered the receiving bottle, while the upper tracing, showing one-third second intervals allowed of the calculation of the time between these two points, or the time which the given weight of blood required in passing through the capillary The two tared bottles containing the blood having been weighed, the volume was calculated from the specific gravity The flow per second (viscosity) was then determined as the result of dividing the known volume by the time (seconds) consumed by this volume in dropping from the capillary of the viscosimeter

OPSONIC TECHNIC

Blood, about 1 c c, obtained from the jugular vein of the animal under observation, was collected and centrifuged in a 5 c c tube, about 0 5 c c obtained from puncture of an ear-vein of the control animal was collected in Wright's bent capillary tube and also centrifuged, about 1 c c of blood of the control animal from a freely bleeding puncture was dropped into a centrifuge tube containing 0 85 per cent sodium chlorid and 1 per cent sodium citrate, mixing thoroughly during collection by inverting the tube after each drop and being careful that the drop in entering the tube should not touch the glass This mixture was centrifuged for five minutes, then the supernatent fluid was poured off and again centrifuged in 0 85 per cent sodium chlorid after shaking This washing was repeated once Even bacterial emulsions were prepared from twenty-four-hour slant agar growths, by the addition of one loop-full of growth to 1 c c of 0 85 per cent sodium chlorid and the emulsion given a few whirls in the centrifuge to throw down clumps of bacteria The translucent upper portion was skimmed off with a pipette, mixed in a watch-glass and transferred to another tube for use The leukocytic cream was obtained as follows After the final centrifugalization of the washed leukocytes was completed, the clear fluid above was carefully pipetted off and the visible upper layer, rich in white cells, was skimmed from the surface of the blood at the bottom by a capillary pipette provided with a medicine-dropper bulb This cream was mixed in a watch-glass in a manner

7 The drop of blood leaving the capillary tip and falling into the neck of the bottle requires a definite time for transit Variations in the position of the drop in transit, at which the carrier was moved and electric connection made, would introduce errors into the time-duration factor of the determination In practice the carrier was always moved to the right or left just as the last drop had disappeared into the neck of the center drip-bottle It was returned to the center just as the last drop had fallen into the weighing-bottle As the same operator always performed this part of the work, this error was reduced to such a degree that the duplicates agreed to within 0 5 per cent, and not infrequently better results than this were obtained

similar to that of the bacterial emulsion and kept in a small tube for use Opsonizing pipettes, according to Wright's technic, were prepared and into each were drawn equal parts of the washed leukocytes, bacterial emulsion and serum, in the order named The contents were blown out into a small watch glass, sucked back and forth five times, then drawn up into the tubes about 5 cm from the tip, the end sealed in the flame and the whole incubated exactly fifteen minutes in the special oven ordinarily employed for this purpose At the end of this time the pipette was removed and the large end capped with a perforated rubber bulb, the sealed end was then broken by file mark and the contents of the tube expelled on the watch-glass and mixed by alternately drawing in and out of the fluid One drop of the mixture was spread on a glass slide in a similar way as for an ordinary blood smear and then stained with Wright's stain The count was made with 1/12 Leitz oil immersion, counting 50 cells

CRITICISM OF THE METHOD EMPLOYED FOR THE OPSONIC DETERMINATION, FROM THE CHEMICAL AND PHYSICAL STANDPOINT

The Wright method has as its foundation the view that opsonizing substances in solution in the serum act on bacteria rendering them more liable to capture by the leukocyte than in the absence of the opsonins The phagocytic power of the white cell is considered to be the same if equally active amounts of opsonizing substance and equal numbers of bacteria are present This notion neglects the fact that phagocytosis as a process is based in a large part on surface-tension changes occurring in the system of substrat (serum) and suspension (bacteria) The tension which exists at the contact surface of leukocyte and serum, and which determines whether a given suspension shall be attracted or repelled, may be altered by chemical changes taking place inside the cell as well as in the serum or suspension Therefore, the character and condition of the leukocyte should be as carefully controlled as its environment [8]

In the first place, the normal leukocytes employed in the determination are washed with 0 85 per cent sodium chlorid solution containing 1 per cent sodium citrate The Δ of such a solution is 0 70° C Hamburger and Hekma[9] have shown that white cells suspended in solutions of sodium citrate (from 1 to 2 per cent) lose their ability to phagocyte If the concentration is not too great or the sojourn of the leukocytes in this solution is not prolonged, the cells recover after resuspension in 0 80 per cent sodium chlorid solution In a later paper, Hekma[9] indicates that leukocytes suspended in a mixture of one part 0 4 per cent sodium citrate and one part horse serum are unaffected

To be sure, the index is a relative comparison of the effect of normal and of test serums on phagocytosis, and as similarly treated leukocytes are used in both determinations, the effect might be considered to be negligible, but there remains the possibility that even the ratio of activity might not be the same if, on the one hand, perfectly normal, and on the

8 Eggers, H E Jour Infect Dis , 1909, vi, 662
9 Hekma Biochem Ztschr , 1908 xi, 177

other, phagocytically less active leukocytes served as controls in the comparison

In the second place, a grave error exists in the assumption that the phagocytosis which takes place in the mixture of normal leukocytes, bacterial emulsion and test serum, forms a true picture of the phagocytosis which is occurring in the body from which the test serum was procured This could be true only if the white cells in the patient were normal This erroneous idea arises from the notion, previously stated, that the leukocytic ability to ingest bacteria is governed entirely from without the white cell The whole environment (i e, the physical character of the blood) of the leukocytes in the test animal is different from that of the controls When removed from its surroundings and compared with normal cells, the test leukocyte and its phagocytic power would undoubtedly vary greatly, even with equal amounts of opsonizing substance and bacteria A true index can only be obtained when control leukocytes and control serum are compared with test leukocytes and test serum To remove this basic error in the method may entail an increase in difficulty of the technic of the determination, but to neglect it leaves the method of suspicious value

Again, since the phagocytic activity of the leukocytes is so decidedly affected by changes in the osmotic pressure of the solution in which they are suspended, it is reasonable to conclude that an examination of their activity should be made in the same ionic concentration (depression of the freezing-point) as that which exists in the blood to be tested, since that is the condition under which leukocytes are phagocyting in the blood of the animal under examination By altering the concentration of the mixture in which the normal leukocytes are to phagocyte in the presence of the serum *in vitro*, a variable condition is introduced which, in all probability, very decidedly influences the resulting phagocytosis Usually the mixture which is incubated is made as follows

1 part washed leukocytes with a $\Delta = 0.545° = 0.85$ per cent NaCl
1 part bacterial emulsion with a $\Delta = 0.545° = 0.85$ per cent NaCl
1 part test serum with unknown Δ = Human blood averages 0.56°
Mixture = unknown Δ = ?

From such considerations it becomes evident that phagocytosis in the test mixture does not take place under the same osmotic conditions as are present in the test serum *in vitro*, with the single exception when the Δ for the test serum equals that of an 0.85 per cent NaCl This fact acts in various ways to render the results of the opsonic index test inconstant Variations in the osmotic concentration of the blood to be tested are reduced by one-third in the preparation of the test mixture for phagocytosis This is an advantage if we consider that the conditions of technic should be as constant as possible from the standpoint of ionic

TABLE 1.—EXPERIMENT 1.—DOG A. CONTROL. ALL CONDITIONS CONSTANT THROUGHOUT

Date	Sp. gr. 1.0—	Δ	K_{co} 10⁻⁴	Viscosity c.c. Per Sec.	Red Cells in Millions	Hemoglobin, %	White Cells	Polymorphonuclear cleavs, %	Lymphocytes %	Large mononuclear clear, %	Eosinophils, %	Trans., %	Opsonic Index
4/10		0.605	40.1	0.04587	6,720	111	9,620	40.8	52.5	1.7	0	3.0	0.79
4/11		0.582	41.0	0.04960	7,144	112	10,110	41.7	50.0	2.1	1.7	1.1	1.01
4/12		0.628	44.4	0.04910	6,112	104	11,160	37.5	53.9	2.3	2.9	3.2	
4/13	580	0.610	48.5	0.05701	5,540	105	13,900	40.7	55.7	0.4	1.6	1.6	1.09
4/14	572		49.2	0.05711	5,800	105	14,800	41.0	52.4	0.8	3.6	2.1	0.91
4/15	565	0.640	50.2	0.05859	5,710	102	16,200	40.6	52.0	1.7	3.2	2.5	0.91
4/16	577	0.625	48.1	0.05840			18,000	41.1	51.2	1.1	2.8	3.8	0.91

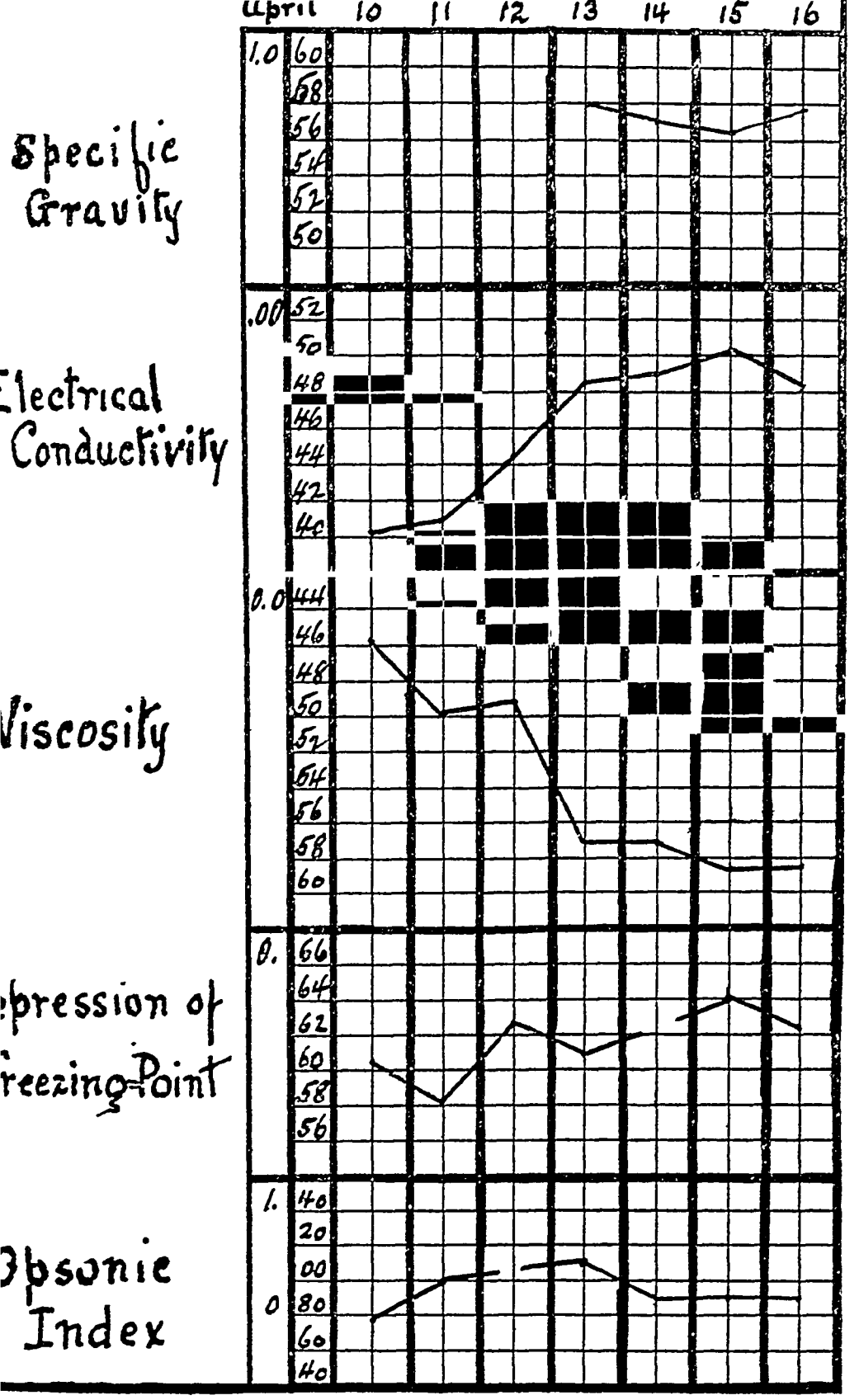

Fig 3.—Experiment 1 Dog A

concentration It acts as a distinct disadvantage, however, in any endeavor to obtain the true effects of the osmotic concentration of the blood on the phagocyting power of the leukocytes

On the one hand, therefore this reduction of osmotic variation in the test acts to make the index more regular and constant, while on the other hand, marked changes are so veiled that they may appear as unexplainable variations

With these points in view, an attempt was made to carry out the testing of the opsonic index in a mixture of bacteria, white cells and serum under the exact osmotic concentration of the experimental blood or serum Hence after the determination of the Δ of the blood the sodium chlorid-citrate mixture employed for the leukocytic cream and the sodium chlorid solution used in the bacillar emulsion were both made of the same ionic concentration

We could then be positive that the control white cells were acting under the same osmotic conditions *in vitro* as were the white cells in the body of the animal from which the blood was drawn for testing This procedure was carried out in all the experiments except in Experiment 1, Dog A. We did not attempt to remove, control or determine the effect of the citrate solution on the relative phagocytosis

OUTLINE OF EXPERIMENT

The animals employed were dogs kept in light roomy cages on a strictly rigid and fixed diet with a definite volume (500 c c) of water per diem The temperature of the room and the amount of exercise were also constant factors About 20 c c of blood were drawn daily at the same hour from the external jugular vein, by aseptic aspiration through the skin The blood was immediately placed in a small (25 c c) fat-extraction flask provided with a rubber stopper through which passed a wire coiled in the flask By this means the blood was defibrinated without coming into contact with much air According to Hamburger[10] when blood is allowed to clot in this manner the defibrinated blood and the whole blood from which it came show no difference in the depression of their freezing-points After defibrination the temperature was raised to 39 C when the blood was strained through absolutely clean gauze into the receptacle of the viscosimeter, and two duplicate determinations of its viscosity made as outlined above This was completed in from ten to fifteen minutes after the withdrawal of blood from the animal As has been stated in the description of the viscosimeter, the blood employed in the determination dripped into a flask belonging to a 10 c c pyknometer After the weight of this for the viscosity determination had been completed, the flask was filled with the defibrinated blood, the ground-glass

10 Hamburger Osmotischer Druck und Ionenlehre, 1, 453

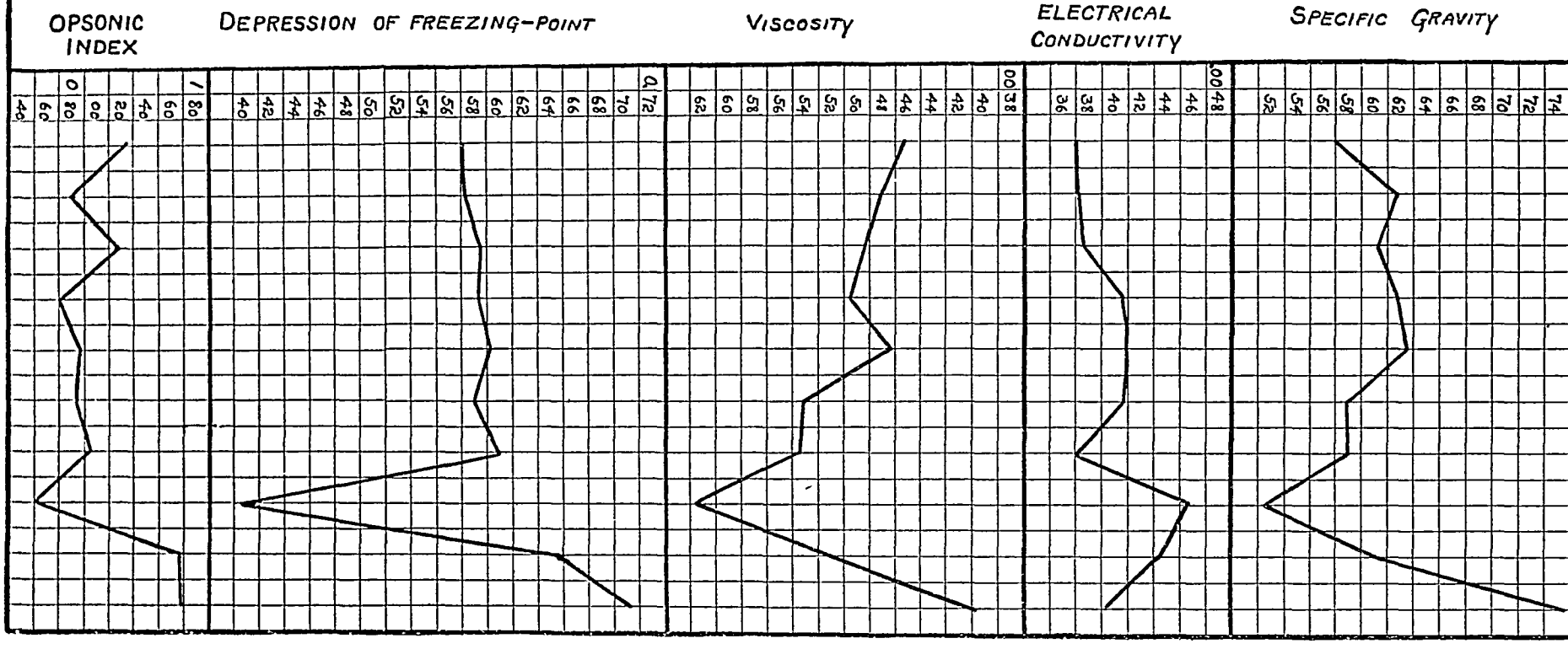

Fig 4.—Experiment 2 Dog B

TABLE 2—EXPERIMENT 2—(DOG B)

Date	Sp gr 1 0—	K_{20} 10^{-4}	Δ	Viscosity c c Per Sec	Red Cells in Millions	Hemoglobin, %	White Cells	Polymorphonuclears, %	Lymphocytes, %	Large mononuclear, %	Eosinophils, %	Trauma, %	Opsonic Index	Remarks
4/29	577	38 0	0 580	0 04587	6,552	110	24,600	89 9	5 8	0 5	0 3	3 5	1 34	Normal diet and conditions Feeding at 9 a m Blood drawn at 2 p m
4/30	626	38 1	0 582	0 04960	6,272	112	13,600	82 3	11 5	1 2	0 9	4 1	0 91	Normal diet and conditions Feeding at 9 a m Blood drawn at 2 p m
5/ 1	612	38 8	0 597		6,504	111	9,110	70 9	19 1	2 8	0 7	6 6	1 13	Normal diet and conditions Feeding at 9 a m Blood drawn at 2 p m
5/ 2	625	41 7	0 592	0 05264	6,168	111	5,600	66 6	23 8	2 6	0 4	6 4	0 80	Normal diet and conditions Feeding at 9 a m Blood drawn at 2 p m
5/ 3	632	42 0	0 602	0 04935	6,816	114	7,880	67 1	27 9	0 9	0 2	3 8	0 96	Normal diet and conditions Feeding at 9 a m Blood drawn at 2 p m
5/ 4	587	41 8	0 590	0 05587	6,840	117	7,520	75 0	18 0	1 3	1 7	4 0	0 93	Normal diet and conditions Feeding at 9 a m Blood drawn at 2 p m
5/ 5	588	38 0	0 613	0 05645	5,904	114	8,920	76 9	16 1	1 1	2 6	3 2	1 04	Normal diet and conditions Feeding at 9 a m Blood drawn at 2 p m
5/ 6	525	46 2	0 405	0 06110	5,332	111	13,660	84 9	11 5	0 2	1 3	2 0	0 60	10 a m 500 c c water besides regular food at 9 a m Blood drawn at 2 p m
5/ 7	604	44 2	0 653	0 05134	7,096	118	12,160	89 3	6 8	0 3	0 9	2 6	1 78	10 a m 125 c c half saturated solution of $MgSO_4$ Regular food at 9 a m Blood drawn at 2 p m
5/ 8	755	40 7	0 713	0 03991	7,128	127	20,200	92 7	3 7	0 8	0 0	2 8	1 77	10 a m 125 c c half-saturated solution of $MgSO_4$ Regular food at 9 a m Blood drawn at 2 p m

thermometer introduced and the specific gravity determination made in the usual way Meanwhile, part of the original defibrinated blood had been placed in the conductivity cell and allowed to cool down to 20 C at which temperature four readings were made at four different resistances by the authors separately The greatest variation in the readings averaged 0 5 mm The electrical conductivity determinations were complete within thirty minutes after withdrawal of blood Finally, the depression of the freezing-point was made in the way previously described Forty minutes, and not infrequently thirty minutes, sufficed to cover the time which elapsed between the withdrawal of the blood and the completion of all the determinations The blood for the red, white, and differential counts and for opsonic work was taken at the time of the aspiration of the blood from the jugular vein The blood was counted by the Thoma-Zeiss apparatus and the differential made with Wright's stain Hemoglobin was determined by the Sahli hemoglobinometer

DESCRIPTION OF THE CHANGES OCCURRING DURING THE EXPERIMENTS

The technic of all the experiments was carried out as previously outlined

Experiment 1, Dog A (Table 1 and Fig 3) was in the nature of a control and ran for seven days Although the temperature diet, fluid and general condition of the animal were kept as constant as possible, it will be seen that somewhat great variations occurred in certain of the individual factors

The results indicate the following

Specific Gravity—The figures are incomplete and give only the last four days of the period They show, however, that this factor was fairly constant during the last of the experiment

Electrical Conductivity—This factor gradually increased at the beginning of the period The last four days are constant and within the limit of experimental error

Viscosity—This value showed a decrease[11] (see Fig 3) continuing through the first three days, during which time the viscosity varied inversely with the electrical conductivity This variation is probably to be explained by changes in the number of red cells The four last days are constant and agree with the electrical conductivity and specific gravity

Depression of Freezing-Point—The figures here are somewhat variable for the whole period The variations, however, are apparently within the normal limits for the dog

Red Cells—The counts for the first three days were somewhat higher than for the last three, when they became constant This agrees with the figures for the viscosity, the smaller the number of red cells the less the viscosity

Hemoglobin figures were high the first three days and low the last three—corresponding to the red-count

Leukocytes—During the whole period of this control experiment, the number of white cells was constantly rising

Opsonic index was low the first day, after that it was fairly constant

The differential count indicated no changes except at the end of the period when there appeared a few normoblasts

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11 The figures indicate volume flow per second and therefore increase as the viscosity decreases

TABLE 3.—EXPERIMENT 3.—(DOG B)

Date	Sp. Gr. 1.0—	Δ	K_{20} 10^{-4}	Viscosity c.c. Per Sec.	Red Cells in Millions	Hemoglobin, %	White Cells	Polymorphonuclears, %	Lymphocytes, %	Large mononuclears, %	Eosinophils, %	Trans., %	Opsonic Index*	Remarks
6/5	561	0.635	46.8	0.03808	5,928	101	17,100	74.1	17.8	0.7	2.4	1.9	0.73 0.98 1.33	Normal diet and conditions. Feeding at 9 a. m. Blood drawn at at 2 p. m.
6/6	524	0.620	51.0	0.05324	5,504	101	14,560	67.2	25.2	0.9	1.3	5.4	0.72 1.09 1.01	Normal diet and conditions. Feeding at 9 a. m. Blood drawn at at 2 p. m.
6/7	483	0.615	63.4	0.07230									0.65 0.84 0.62	Normal diet and conditions. Feeding at 9 a. m. Blood drawn at at 2 p. m.
6/8	513	0.645	55.1	0.06794	5,074	98	17,510	70.9	17.7	1.0	2.9	7.3	0.24 0.31 0.57	Normal diet and conditions. Feeding at 9 a. m. Blood drawn at at 2 p. m.
6/9	494	0.595	55.8	0.07560	4,472	84	19,820	83.0	13.0	0.2	0.9	2.9	0.72 0.28 0.25	10 a. m. 500 c.c. water, besides regular food at 9 a. m. Blood drawn at 2 p. m.
6/10	468	0.585	58.9	0.07910	4,896	86	22,200	80.5	15.3	0.6	1.5	2.0	0.99 0.88 0.69	10 a. m. 500 c.c. water, besides regular food at 9 a. m. Blood drawn at 2 p. m.
6/11	496	0.615	57.9	0.06205	4,892	88	18,160	71.9	20.8	0	1.9	2.4	0.90 0.78 0.81	10 a. m. 125 c.c. half-saturated solution of $MgSO_4$. Regular food at 9 a. m. Blood drawn at 2 p. m.

*The figures in the upper left hand corner apply to *pyocyaneus*, those in the center to *typhosus*, those in the lower right hand corner to *Staphylococcus aureus*.

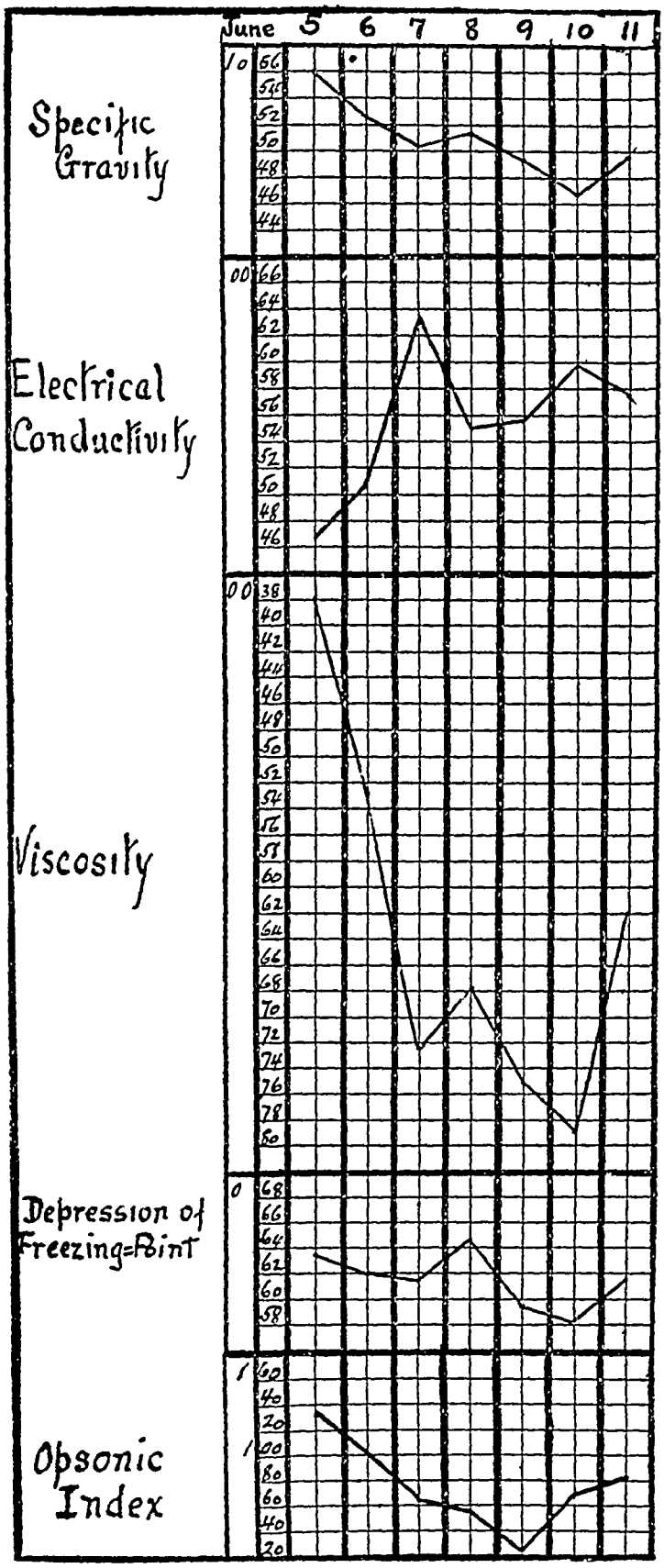

Fig 5—Experiment 3 Dog B

EXPERIMENT 2 (*Dog B*, Table 2 and Fig 4) continued for ten days—the first seven (April 29 to May 5, inclusive) being a duplicate of Experiment 1

The first seven *control* days in this experiment agreed in all essential details with those of the previous one

The Δ remained quite constant, the specific gravity and electrical conductivity indicated slight normal variations, which, however, paralleled each other

The viscosity tended to decrease somewhat, and this occurred in spite of the constancy of the red count, the white cells decreased at first, only to rise again toward the end

The leukocytes remained constant also after the first days, when they were increased

The opsonic index suffered certain variations which were sufficiently slight however, to serve as excellent controls for the following three days

May 6, at 10 a m, the animal was given 500 c c of water by stomach-tube and blood was withdrawn at 2 p m The examination of this indicated marked changes from the normal, the specific gravity, Δ, and viscosity had decreased and the electrical conductivity had increased The red count and the opsonic index both fell The other factors remained constant

The next two days (May 7 and 8) at 10 a m, the animal received 125 c c of half-saturated magnesium sulphate solution and the blood was withdrawn at the usual time On the 7th, the factors of the blood had tended to resume their normal levels The Δ was somewhat increased above normal, however, but the electrical conductivity still remained high, the viscosity and specific gravity seemed normal, while the red count was quite high The opsonic index had reversed itself and increased decidedly over the normal The results for the second day of the administration indicated a continuation of the trend of changes shown on the first day and a simple accentuation of them The specific gravity, Δ, viscosity and hemoglobin content became very high, the electrical conductivity remained normal and the red count was still high The opsonic index also continued at its high level

EXPERIMENT 3—Dog B (Table 3 and Fig 5) This was a duplicate of the previous experiment, except that the control period lasted but four days (June 5, 6, 7, and 8)

Three organisms (*B pyocyaneus*, *B typhosus*, and *Staphylococcus aureus*) were employed for the opsonic index and, as can be seen by a glance at the table, the change which occurred affected all three to approximately the same degree

The figures for the various factors during the control period showed somewhat greater variations than in the previous controls Whether this was due to the shortness of the period or to some other factors is difficult to decide definitely, however, an examination of the control periods in the two previous experiments indicates the greatest irregularity during the earlier days It is noticeable, however, that the Δ was higher and the opsonic index and the viscosity after the initial day considerably lower than is usually found for normal dogs The low index is particularly evident on the last day of the control period, the figure for *Staphylococcus aureus* was about the same as the previous day, but those for *B pyocyaneus* and *B typhosus* were very low

On the 9th and 10th, 500 c c of water were given by a stomach tube in addition to that in the food The effect is not so marked as in the previous experiment

The specific gravity, Δ, viscosity and opsonic index and red-counts show decreases on the 9th, which become more marked on the 10th with the exception of the values for the opsonic index This increased somewhat The electrical conductivity followed the physical factors, but, as is the case usually, in the inverse direction

On the 11th, at 9 00 a m, 125 c c of magnesium sulphate were given by tube The blood drawn at 2 00 p m showed decided changes from the previous

day The specific gravity, Δ, opsonic index, and viscosity had increased, the electrical conductivity became somewhat lower, while the red-count was unchanged The dog died the next day before blood could be drawn, probably as the result of an attempt to push the administration of the magnesium sulphate

EXPERIMENT 4 —Dog E (Table 4 and Fig 6) This experiment consisted of a control period of three days, there being a lapse of seventy-two hours between the second and third control days, omitting the examination of blood on June 11,

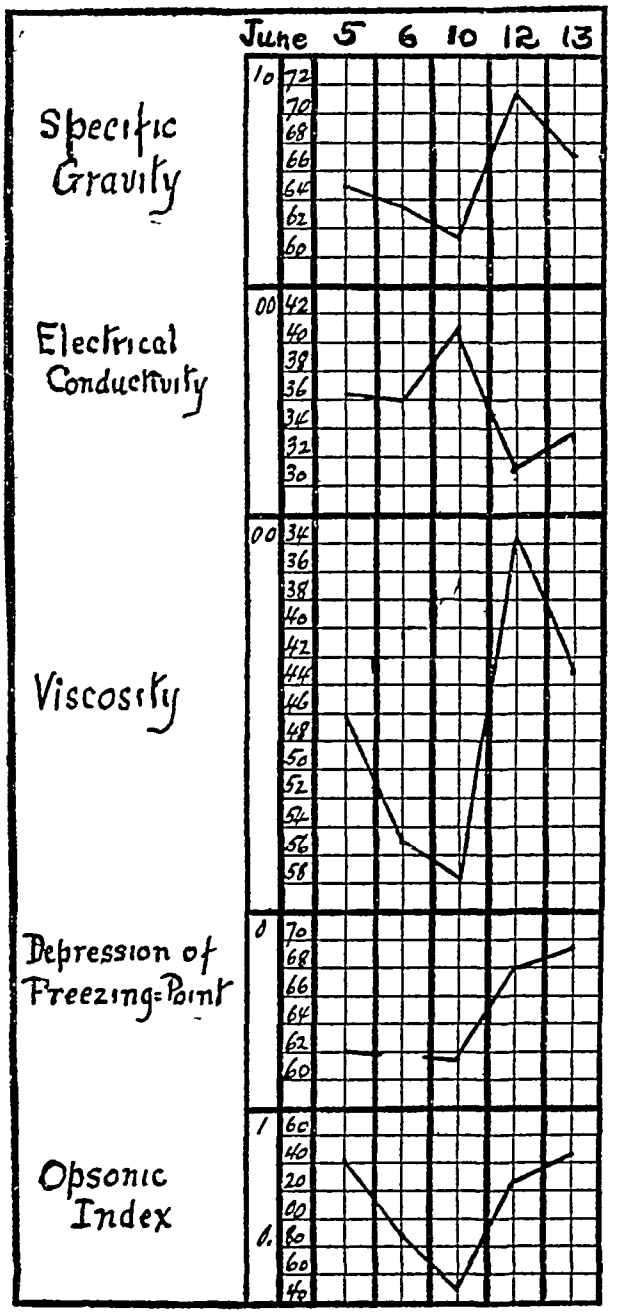

Fig 6 —Experiment 4 Dog E

magnesium sulphate (125 c c) was given on the 12th and 13th Blood was drawn on the second day (June 12) at 2 00 p m and on the following day after the last administration of the magnesium sulphate The short interval of time which intervened between the ingestion of the salt and the removal of the blood did not allow the effect of the administration to show itself in the blood

The three control days gave fairly concordant, although variable, results, the values for the specific gravity, Δ, viscosity and opsonic index ran parallel while those for the electrical conductivity were inversely proportional One point,

TABLE 1—EXPERIMENT 1—DOG E

Date	Sp gr 1 0—	Δ	K_{20} 10^{-4}	Viscosity c c Per Sec	Red Cells in Millions	Hemoglobin %	White Cells	Polymorphonuclears %	Lymphocytes %	Large Mononuclears, %	Eosinophils %	Trans %	Opsonic Index*	Remarks
6/ 5	649	0 620	36 3	0 04814	7,872	135	9,520	56 2	25 3	1 3	15 3	1 9	0 84 1 05 1 12	Normal diet and conditions Feeding at 9 a m Blood drawn at 2 p m
6/ 6	638		36 0	0 05492	8,976	135	10,400	16 6	27 1	0 9	21 5	3 9	1 14 0 80 0 88	Normal diet and conditions Feeding at 9 a m Blood drawn at 2 p m
6/10	612	0 615	41 1	0 05764	8,016	123	10,300	72 5	15 6	0 7	8 7	2 5	0 66 1 26 0 51	Normal diet and conditions Feeding at 9 a m Blood drawn at 2 p m
6/12	714	0 680	31 3	0 03419	9,848	146	24,640	90 0	5 8	0 6	1 8	1 8	1 33 1 15 1 26	Feeding at 9 a m At 10 a m 125 c c half-saturated solution of $MgSO_4$ Blood drawn at 2 p m
6/13	670	0 695	33 5	0 04306	8,008	121	16,640	69 1	14 6	1 6	11 6	2 9	1 45 1 02 1 47	Feeding at 9 a m At 10 a m 125 c c half-saturated solution of $MgSO_4$ Blood drawn at 11 a m

*The figures in the upper left hand corner apply to *pyocyaneus*, those in the center to *typhosus*, those in the lower right hand corner to *Staphylococcus aureus*

however, must be noted, on June 10 (the last control day and distant three days from the other two), the figures for opsonic index, specific gravity and viscosity were the lowest and the electrical conductivity the highest for the whole experiment On the day (June 12) when the action of the magnesium sulphate was most pronounced the specific gravity, Δ, viscosity and opsonic index were largely increased The electrical conductivity became lowered On the 13th there ensued a tendency for the figures to return to the normal, with the exception of the Δ and opsonic index, the reason for which is explained above

CONSIDERATION OF THE RESULTS

The one fact which stands out most clearly in summing up the results, presented here, is the marked variation in the opsonic index following changes in the osmotic concentration of the blood The close coincidence of the two factors is so evident that there can be no question as to their relation as cause and effect Undoubtedly the revised physico-chemical technic employed in the performance of the test for the opsonic index has served to accentuate the results and the effects of such altered ionic concentration That this effect on the index has been imperfectly recognized by the laboratory clinician cannot be denied In evidence of this we see the various attempts instituted to decrease, by perfected technic, the "normal variations" which constantly occur, or the clinician regulates the diet (water ingestion) of the patient under observation and proscribes any excessive exercise (loss of water by perspiration) Diarrhea unaccompanied by a corresponding increase of water ingestion must also exert a positive influence for opsonic variation

Of interest in this connection is the work of Murray, Williams and Orr,[12] who attempted to get evidence of a local production of opsonins by the use of bandages on the limbs, thus excluding and obstructing certain portions of the circulation Their results lacked such degree of uniformity that the attempts were given up Such procedures were well calculated to originate osmotic alterations in the blood present in the circumscribed areas, similar to those which we produced throughout the body, and the wide variations in index which they observed are easily explained by our results

In Figure 5 (chart of Experiment 3, Dog B), it will be noticed that on the first day, as the result of water ingestion, the opsonic index decreased with a slight decrease in Δ, on the following or second day of water ingestion the Δ continued to decrease but the index underwent a rise which brought it back to normal On this day, therefore, the opsonic index increased with decreasing osmotic concentration, which is the reverse of the usual relation Mention should be made of one factor which may, in part, account for the apparent discrepancy The animal got up a marked diarrhea which evidenced itself in a much slighter decrease in osmotic concentration of the blood than would ordinarily have

12 Murray, Williams and Orr Biochem Jour 1909, iii 353

followed increased water ingestion, the other physical constants show a similar lack of positive effect The fact that the increase in the index showed itself in all three organisms employed would point strongly against any error having crept into the technic of the determination

In Experiment 3 (Dog B) the three organisms utilized for the determination of the index showed a general agreement Apparently the same gross conditions which affected their proneness to be engulfed by the white cell acted on all three in the same manner In Experiment 4 (Dog E), with the exception of the first control day, *Staphylococcus aureus* and *B pyocyaneus* ran parallel while *B typhosus* followed an apparently inverse order This variation in the different organisms falls in line with some preliminary studies which we have made with the view to determining the effect on the phagocytic power of a variety of organisms, as the result of alterations in the osmotic conditions of the medium We have been able to note that for all organisms there is apparently a maximum (optimum) condition or degree of osmotic concentration at which the organisms are most markedly phagocyted From this optimum phagocytosis decrease in both directions, i e, when the osmotic concentration is either increased or decreased from the maximum This optimum condition for maximum phagocytosis varies for the different organisms, and this therefore explains why, when different organisms are employed for the same series of serum varying in osmotic concentration the opsonic index according to each should not necessarily run parallel This possesses much importance in relation to the technic of performing the test, especially when taken into consideration in connection with the effect of altered ionic concentration on the opsonic values

It is important to note in another connection that the electrical conductivity varied inversely with all the other physical factors i e, as the specific gravity, Δ, and viscosity decreased or as the blood suffered a dilution the electrical conductivity increased and *vice versa* The determination of this latter factor in the blood gives evidence of the degree of dissociation of the inorganic salts or electrolytes Hamburger was the first to call attention to the fact that in the blood the inorganic salts existed in an incompletely dissociated condition, and that by dilution dissociation was increased Oker-Blom,[13] Bugarszky and Tangl,[14] and Viola,[15] in experiments with serum *in vitro,* showed that by dilution the "physiological" conductivity increased on continued dilution Oker-Blom also indicated that the blood proteins markedly affect the electrical conductivity of the electrolytes This factor is depressed by 2 5 per cent on account of each gram of protein in 100 c c of blood This, then forms a second and additive factor, in that a dilution of the blood

13 Oker-Blom Arch f d ges Physiol (Pfluger's), 1900, lxxix, 510
14 Bugarszky and Tangl Arch f d ges Physiol (Pfluger's), 1898, lxxii, 531
15 Viola Estratto del periodico Revista veneta di science mediche, 1901, xviii, No 8

decreases this depressive effect on the electrical conductivity, the result is increased ionic conduction These facts seem sufficient to explain the results obtained by us Lastly, we do not fail to recognize the fact that in the experiments in which magnesium sulphate was given *per os,* a certain criticism might be raised that the phagocytosis was affected by the magnesium sulphate after absorption as well as by the changed condition in osmotic concentration [8] This is true only in part, for it must be remembered that the concentration of the blood, resulting from the ingestion of a single dose of magnesium sulphate, is brought about by the withdrawal of water from the blood in virtue of the osmotic pressure exerted in the intestine by the salt on account of its slow absorption We must grant then that during the initial concentration of the blood, very little of the salt can be present in the blood and its effect is negligible When this salt finally makes its appearance in the blood, it exerts an osmotic pressure sufficient to withdraw fluid from the tissues and as a result of this, the blood becomes more dilute and a *decreased* Δ occurs

Bearing all this in mind, the attempt was made to time the ingestion of the salt so that the usual withdrawal of blood would occur at a period when slight absorption of the salt had occurred and the diarrhea had advanced sufficiently to result in an increased ionic concentration of the blood If blood had been drawn later on in the day, in all probability it would have been noticed that a dilution had occurred from the fluids of the tissues sufficient to cause the concentration to return to normal or even below it perhaps

CONCLUSIONS

The facts brought out in these experiments bring into prominence certain neglected factors which bear on the accuracy and variability of the opsonic index As a result of experimentally altering the concentration of the blood, great variations in the opsonic index made their appearance The changes thus induced are but magnified pictures of what the blood is undergoing normally in the course of the day following excessive eating, drinking, or exercise On the other hand since the ionic concentration of the phagocyting mixture possesses such a marked effect on the ability of the white cell to take up bacteria, it seems only reasonable that in accurate determinations of this phagocytic power, the experimental conditions, under which the white cells are required to act *in vitro,* should correspond as nearly as possible to the conditions under which the leukocytes of the experimental animal exist *in vivo* This can only occur when the experimental solutions employed correspond in concentration to that of the serum from which the white cells were removed Since these variable factors have never sufficiently been realized, it is not strange that the so-called normal opsonic index is an irregular affair

These results should also lead us to inquire whether the variations in opsonic index brought about by the injection of vaccines, with the assumed increase in the amount of opsonins in the blood, have not as their basis alterations in the physical factors of the blood, and whether the preparation of the bacteria, so that they may be more readily engulfed by the white cell, may not consist in a large part in changing the surface tension of the system consisting of white cells, substrate and suspension We believe that much experimental work performed along these lines indicates that the latter explanation is probably true

SUMMARY

1 Variations in the physical factors of the blood were produced by the ingestion of water (dilution) or of magnesium sulphate (concentration)

2 Decreased concentration of the blood showed itself by a lowering of the values for specific gravity, Δ, and viscosity, and an increase in the electrical conductivity Increased concentration brought about a reversal of these changes

3 The opsonic index was determined by allowing phagocytosis to take place in a bacterial emulsion of the same ionic concentration as that of the serum which was under observation This increased accuracy in duplicating the conditions *in vivo* should result in obtaining a more faithful picture of the actual ability of the white cells while in their natural environment

4 In the three experiments the values of the opsonic index for *Staphylococcus aureus* ran parallel with variations in the specific gravity and Δ of the blood, and inversely with the electrical conductivity In the third experiment, in which two other organisms were similarly tried, the results do not agree In explanation of this it is suggested that the optimum and minimum points of phagocytic ingestion for bacteria of different kinds are not coincident

5 In all probability, therefore, a large portion of the so-called normal variations in the opsonic index are due to changes in the physical characteristics of the blood, and other variations in disease may be explained, in part, in a similar manner

338 East Twenty-Sixth Street

A STUDY OF THE BLOOD AND FECES BEFORE AND AFTER BILATERAL NEPHRECTOMY AND DOUBLE URETERAL LIGATION, AND OF THE URINE SECRETED AFTER RE-IMPLANTATION OF THE URETERS*

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NEW YORK

Much experimental evidence has been advanced in the endeavor to determine the immediate cause or causes concerned in the death of animals whose kidneys have been removed or whose ureters have been ligated, and as the result of apparent differences in the duration of postoperative life, attempts have been made to ascribe to the kidney a function other than that of excretion in the general sense That the simple ligation of the ureter resulted in the stoppage of urine formation but did not interfere with the production of an internal secretion, presumably necessary to the life of the animal, seemed a logical conclusion from the notion that animals lived longer with their ureters ligated than when both kidneys were extirpated These statements find considerable support from clinical findings in cases in which both ureters were accidentally ligated or in which a persistent anuria existed

Recent experimental work does not, however, bring additional evidence that any such difference exists In fact, one finds statements to the effect that ureteral ligation leads to a more rapid death than does double nephrectomy The older investigators ignored several very important experimental details which affect the duration of life in as great a degree as does the absence of the kidney function The character of the diet, whether protein foods are included, whether the animal is given water or not, or deprived entirely of food with or without water, all these conditions influence the length of postoperative survival [1] When comparative experiments are carried out in which these conditions are kept constant, or when one compares only the work of different investigators where comparable conditions existed, it becomes evident that within the limits of error for such work, the postoperative survival of the animals is valueless as a criterion for comparison of the effect of ureteral ligation and

*This work was performed in the Department of Physiological Chemistry Bender Hygienic Laboratory Albany N Y the expenses were defrayed by Dr John A Sampson Albany N Y

1 Koranyi Berl klin Wchnschr 1899 xxxvi 97 and 781 Strubell Wien klin Wchnschr, 1901 xiv 689

double nephrectomy Some differences do exist, but as to their exact cause nothing definite may be said from the results of the present investigation

If for the sake of argument, we admit that the kidneys do secrete into the blood a substance or substances necessary for the continued existence of the animal, this beneficial effect becomes neutralized by the baneful result of the non-removal of products of metabolism

Investigations into the cause of death in both types of operative interference have followed two lines of procedure Either the blood-changes following double nephrectomy and double ligation have been studied and compared, or attempts have been made to prolong or shorten the life of the animal by blood-letting or intravenous injection of various salt solutions, organ extracts or blood from other animals of the same species To all such evidence must be added that obtained from the clinical study of cases of nephritis with partial or complete anuria

It has long been felt that the changes occurring in the blood were of a character not sufficiently gross to allow of detection by chemical examination, nor was it possible to obtain amounts of blood necessary for a complete study of the majority of substances which might undergo variations following such operative procedure This has brought about a turning of experimental methods in the direction of physico-chemical measurements, among which may be mentioned the determination of the depression of the freezing-point (Δ), of the electrical conductivity (K), of the viscosity, of the specific gravity, of the water content by means of the refractometer, and of corpuscular variations In some few instances the sodium chlorid, protein, residual (non-coagulable) nitrogen or ash content of the blood was determined for the normal animal and just before death, following operation

Unfortunately, the great majority of these experiments were carried out on rabbits The results which have been obtained on these animals in the study of nephritic edema and similar conditions have indicated clearly that alterations in the renal function bring about changes in the blood and tissues which cannot be induced in some other animals, e g the dog It therefore becomes questionable whether the rabbit may be utilized in explaining conditions appearing in man Such marked physiological differences exist between the herbivora and carnivora or omnivora that it seems most advisable to employ dogs or, better still, monkeys in the study of renal function and the effects produced by its absence

In attempting to obtain a clear insight into the present state of the question under discussion one is met with a mass of data of a very conflicting character The cause of this has been alluded to above It seems, therefore, unwise to detail at further length experimental work of somewhat questionable value, and consequently it will suffice to indicate

the general trend of evidence which has been accumulated by the different investigators.

Little of significance can be deduced from the study of the length of life following operation, the time given varying from forty-eight to 108 hours It seems that the diet[1] and general conditions of the animal influence this factor most markedly On one point there is general agreement namely, that following the operation, the Δ of the blood increases gradually from the normal and reaches its maximum at death Since the figures (Δ) for normal rabbits' or dogs' blood or serum vary quite considerably, it is to be expected that the lethal Δ should also be inconstant The highest values[2] are 1 15 C Others vary according to the normal figure obtained and the length of life of the animal The average figures for a life of from eighty to one hundred hours would be 0 80°-0 90° C With reference to these facts it must be stated that apparently no parallel exists between the molecular concentration of the blood and the death of the animal, some animals remaining in good condition with a very high Δ Apparently in nephritis, also, the molecular concentration is not characteristic of any one form of the lesion[3]

This has led to an examination of changes in the electrical conductivity, but here the investigators also differ in their results One fact is established, namely, that no parallelism exists between the molecular concentration and the electrical conductivity[4] The latter factor (K) is quite variable, even in normal individuals, the reason for this is not difficult to locate Other factors remaining constant, a simple hydremia or dilution of the blood would tend to *increase* K in virtue of the consequent increased dissociation This condition could also be brought about by an increase in electrolytes The electrical conductivity of the blood is occasioned almost entirely by dissociated inorganic salts, Bugarszky and Tangl[5] consider that 7 per cent is caused by sodium chlorid, 3 per cent by phosphates and the remainder by sodium carbonate or bicarbonate A *decrease* in conductivity can be brought about by a decrease in the amount of ionized inorganic compounds or by a decrease in the degree of dissociation which might occur without change in the absolute quantity of the salts This depression of electrolytic dissociation, as it occurs in the blood, owes its origin to the presence of the colloidal substances (proteins) in the serum If a percentile increase in these compounds occurs the conductivity is decreased (2 5 per cent for every 1 per cent increase in protein[5]) As the result of a consideration of these facts, especially in connection with the observed lack of parallelism between K and Δ

2 Waldvogel Arch f exper Path u Pharm, 1901 xlvi, 41

3 Cohn T Mitt a d Grenzgeb d Med u Chir, 1906, xv, 27

4 Ceconi Arch per le Sc Med 1902, xxvi, 395 Segale, M Boll R Accad Med de Genova, 1906 xxi 220 Bickel Ztschr f klin Med, 1902, xlvii, 481

5 Bugarszky and Tangl Pfluger's Arch, 1898 lxxii, 531

the majority of investigators feel inclined to believe that the increase in molar concentration is to be attributed to non-dissociated compounds It must be remembered, however, that if there occurred simultaneously an increase in substances (protein) tending to depress electrolytic dissociation, and an increase in compounds (salts) capable of augmenting dissociation, the figure for K would remain *unchanged* and the presence of both bodies be masked This feature of the question will be considered in connection with the findings of the present paper

In this connection it must be noted that clinical evidence on Δ and K is conflicting, in nephritis with and without uremic symptoms some authors indicate that in perhaps the majority of cases, the increase in molar concentration accompanied the onset of the most marked symptoms of uremia Such cases nevertheless show normal Δ, and it is emphasized that a high Δ does not necessarily bring about uremic conditions The K remains normal even during the most pronounced renal insufficiency [6]

The results of viscosimetric determinations following renal insufficiency or operative procedure are somewhat conflicting The cause for this is to be ascribed to the great variety of instruments employed and to the difficulty encountered in keeping constant the conditions necessary for obtaining comparable figures [7] No specific statements can be made with reference to the variation of the viscosity alone or in relation to the other factors Segale[8] showed that neither vomiting, which is a common symptom following either operation, nor the amount of fluid given to the animal, influences the viscosity of the blood in a specific way for any length of time Sometimes the viscosity is greater and at other times less, these variations appear without evident cause but do not accompany changes in the number of red or white corpuscles [9] Apparently, the viscosity is the result of the interreaction of many factors, the effects of most of which are at present unknown to us

Little attention has been paid to the specific gravity since it was early found that the determinations showed great irregularities unless accurate methods were employed In general, this factor parallels the increase in Δ ordinarily observed and the viscosity,[10] although the latter statement is denied by Hirsch and Beck [11] Attempts to induce evidence that the beneficial effects of bleeding on uremia owed their origin to an

6 Poly, F Deutsch med Wchnschr, 1904, xxx, 839 Engelman, Fritz Mitt a d Grenzgeb d Med u Chir, 1903, xii, 396 Allaria, G B Jahrb f Kinderh, 1906, lxiii, 74

7 Bence Ztschr f klin Med, 1905, lviii, 203 Bachman Deutsch Arch f klin Med, 1908, xciv, 409

8 Segale Boll R Accad Med de Genova, 1906, xxi, 220

9 Burton-Opitz (Pflüger's Arch, 1907, cxix, 359) and Determann (Ztschr f klin Med, 1906, lix, 283) deny this statement

10 Kottman, K Correspondenzbl f Schweiz Aerzte, 1907, xxxvii, 97 and 120

11 Hirsch and Beck Deutsch Arch f klin Med, 1901, lxix, 593, 1902, lxxii, 560

augmented and bettered circulation as the result of decreased viscosity, indicated that the viscosity of both the whole blood and the serum underwent a decrease following the removal of from 50 to 100 c c of blood [12]

The extent of the hydræmia has been determined either by direct analysis or by the refractometer [13] In most cases of renal insufficiency in man the results point to an increase in water content of the blood Bence,[14] also working with nephrectomized rabbits, showed that the daily loss in weight was less than in the case of intact animals, and that this retention of water was more than could be accounted for by the retained urine Most authors explain this condition by an alteration in the water equilibrium and the passage of water from the tissues into the circulating fluid If water is given the hydræmia is increased (rabbits[15]) Brandenstein and Chajes[16] incline to the assumption that the retained sodium chlorid remains in the blood and with it holds a larger quantity of water in the circulating fluid

Concerning variations in the sodium chlorid, urea and non-coagulable nitrogen content of blood, few observations are available Van Maanen[17] found that, as the result of tying both ureters, the amount of chlorin does not increase but the rest-nitrogen becomes augmented Some clinical observations[18] point to an irregularity in the amount of sodium chlorid in different forms of renal insufficiency, but indicate that when uræmic symptoms appear the urea content of the blood is always found to be greater than normal

Finally, several attempts have been made to prolong the life of the animals following either double nephrectomy or double ligation of ureters After bilateral nephrectomy transfusion of from 100 to 175 c c normal saline does not affect any material difference in the length of life [19] This is contrary to the results of Vitzou,[20] who increased the average duration of life from seventy-one to 164 hours as the result of transfusion On the other hand, Couvée[21] pointed out that if in nephrectomized animals soon after operation, the blood of nephrectomized animals of relatively long standing be injected, there is no effect The injection of defibrinated blood- and tissue-extracts apparently prolonged but slightly the period

12 Schreiber and Hagenberg Centralbl f Stoffw 1901, ii, 287
13 Strubell Deutsch Arch f klin Med, 1901, lxix, 521 Strauss and Chajes Ztschr f klin Med, 1904, lii, 536
14 Bence, J Ztschr f klin Med, 1909, lxvii, 69 Strauss, H Ztschr f klin Med, 1906, lv 500 Georgopulos, A Ztschr f klin Med 1906, lv, 411
15 Bence and Savonat Rev de Med 1907, xxvii, 620
16 Brandenstein and Chajes Ztschr f klin Med, 1905, lvii, 265
17 Van Maanen, A Dissertation, Utrecht, 1905 Also Maly's Jahresber 1905, xxxv 381
18 Javal and Adler Compt rend Soc biol, 1906, lxi, 235
19 Crile, G W and Cole H P New York Med Jour, 1907 lxxxvi 145
20 Vitzou Journ de Physiol et Path générale, 1901 iii, 901 and 926
21 Couvée H Ztschr f klin Med 1904, lv 311

of life These results were repeated by van Maanen[17] on animals with double ligation of the ureters The injection (direct transfusion) into animals recently operated on, from animals operated on eighty-six hours previously, seems to increase the postoperative life from 20 to 50 per cent Saccharose solutions exhibited a more beneficial effect than 0 9 per cent sodium chlorid No difference could be observed when edematous fluids from nephritics or blood-serum from eclamptics were introduced in the circulation The nitrogen content of operated animals was found to be normal

Work of somewhat different character was performed by Ignatowsky[22] on rabbits The urine was studied after single nephrectomy as well as the length of life following the removal of the second kidney The extirpation of one kidney brought about a decrease in chlorin elimination with an increase in the urea output The animal died two or three days after the second kidney was taken out Ligation of one renal artery caused results somewhat similar to single nephrectomy, after the second week however, the animal commenced to lose weight and there appeared toxic symptoms which the observer ascribed to absorbed products of necrosis Ligation of the second artery killed in from two to three days Ligation of veins gave almost analogous results After the ligation of one ureter the increase in size of the kidney, as determined by percussion, was considerable and at autopsy there existed a hydronephrosis The animals which survive the single ligation begin to lose weight after two or three weeks and eat less The second ligation kills in from three to four days

In view of the extreme divergence in the results obtained by the various investigators interested in the problem, it appeared of sufficient interest to attack the question from a somewhat different direction

The original plan of the investigation consisted in an attempt to study and compare (1) the blood of dogs before and after double nephrectomy and (2) the blood and urine of dogs before double ureteral ligation the blood during the ligation and the blood and urine subsequent to the release of the ligature and reimplantation of the ureters in the bladder

Early in the work, on double ureteral ligation, it became evident that infection was a weighty factor in the death of the animals A number of experiments were carried out in the hope of locating the course of this infection which brought about death within two to four days The locus was apparently in one or both of the ligated kidneys, this seemed to exclude the wound as the point of origin The results of the search will be detailed in another paper, but the simple explanation of the difficulty seems to lie in the fact that in the course of the operation, and after the ligation of the ureters, the peritoneum was not sutured and the infec-

22 Ignatowsky, A Compt rend soc Biolog, 1905, lviii, 10 and 130

tion in the peritoneal cavity, ordinarily taken care of at that point, passed through the opening in the peritoneum and retroperitoneally found its way up the ureters to the kidney where a *locus minoris resistentiæ* existed In subsequent experiments, in which the peritoneal cut was sutured following the ureteral ligation, no infection was observed Some few results were obtained, however, in the early experiments in which the ligatures were released and the ureters reimplanted before the infection had sufficiently advanced to preclude recovery

In the investigation it was therefore found necessary to confine ourselves largely to the changes occurring in the blood and feces before, and during, double nephrectomy and ureteral ligation, with some observations on the character of the elimination following release of the ligature and elimination into the intestine following the surgical interference In the ligation experiments without subsequent reimplantation, it must be remembered that the animals died or were killed during a more or less marked renal infection, since subsequent results, without infection, show the same changes, we feel justified in assuming that the infection was without influence and hence make use of these experiments

The results will be considered as follows

I Double nephrectomy — analysis of the blood before and after operation

II Double ureteral ligation — analysis of the blood before and after operation

III Examination of urinary changes before ligation and following release of ligature, and on account of the possible elimination of water, purin bases and uric acid into the intestines, the feces of some of the animals were analyzed

PLAN OF EXPERIMENTS

By means of a large hypodermic needle and syringe, the blood was drawn aseptically by aspiration from the external jugular vein daily at 2 p m The preparation and analysis took place in exactly the same way and the same methods and apparatus were employed as outlined in other experiments,[23] with the exception that, at the end of the determination of the physical constants, the blood was precipitated with ten times its volume of alcohol and allowed to stand over night The clear fluid was then filtered off and the coagulated blood protein washed and ground up in a mortar repeatedly with 95 per cent alcohol The original fluid and washings after evaporation to a few cubic centimeters were taken up in water and made up to 50 c c Of this, 25 c c were taken for Kjeldahl determination (duplicates) and the other 25 c c saved for the determination of the chlorids (neutralization and direct titration with silver nitrate and potassium chromate)

23 Jackson and Hawn THE ARCHIVES INT MED this issue

The animals were kept in approximate nitrogenous equilibrium with a low protein diet of 10 gm casein, 100 gm cracker-dust, 20 gm lard and 500 c c of water Attention has already been called to the importance of the diet in this connection As will be seen from the tables, the animals, however, ate little or nothing following the operative procedures The operations were carried out with the usual surgical asepsis and technic and were performed by Dr J A Sampson, to whom we wish to express our gratitude

I DOUBLE NEPHRECTOMY

Three experiments were successful

EXPERIMENT 1 (Dog 1) —Control-blood was drawn and analyzed on December 23, 25, and 28 The operation occurred December 29, at 11 a m, and the animal survived until the night of January 1-2, i e, 83 93 hours Blood was drawn on December 30 and 31 and January 1 No chlorid or nitrogen determinations were carried out, and the viscosity figures are incomplete

TABLE 1 —BILATERAL NEPHRECTOMY, EXPERIMENT 1, DOG 1*

Date	Sp Gr 1 0—	Δ	K_{10} '	Viscosity c c per sec	NaCl %	N %	Remarks
12/23	567	0 605	47 1	2 280			Food and 500 c c water
12/25	561	0 575	49 3				Food and 500 c c water
12/28	551	0 580	52 7	2 076			Food and 500 c c water
12/30	483	0 560	58 0	2 018			Operation Dec 29, 11 a m, after operation ate practically nothing, given 500 c c water
12/31	515	0 595	57 3				500 c c water
1/1	545	0 660	55 5	2 247			500 c c water

*Death on night of January 1-2 Postoperative life eighty-three to ninety hours

The results indicate that on the day following the operation, the specific gravity and Δ underwent a temporary decrease and the electrical conductivity a corresponding increase On the two succeeding days the specific gravity and Δ gradually increased and the electrical conductivity decreased The viscosity showed little or no change

EXPERIMENT 2 (Dog 4) —In this case there were three control days, January 12, 14 and 16 The blood for the third day was drawn just before the operation at 11 a m The animal survived until January 20, when in the afternoon he appeared so weak that he was anesthetized and killed at 4 p m, 101 hours

The same changes occurred here as in the previous experiment except that the Δ did not fall below normal on the first postoperative day The subsequent daily increase of specific gravity and Δ and decrease of electrical conductivity occurred until death It will be noticed, however, that K increased markedly on the first day following the operation and

had not reached its normal level when death occurred The viscosity, also, suffered no variation except on Dec 18, when it was very low [24]

TABLE 2 —BILATERAL NEPHRECTOMY, EXPERIMENT 2, DOG 4*

Date	Sp Gr 1 0—	Δ	$K_{20}10^{-4}$	Viscosity c c per sec	NaCl %	N %	Remarks
1/12	586	0 625	45 4				Food and 500 c c water
1/14	593	0 615	46 7	2 149	0 365	0 054	Food and 500 c c water
1/16	580	0 615	43 0	2 160	0 407	0 044	Food and 500 c c water Operation Jan 16, 11 a m
1/17	480	0 655	63 5	2 114	0 651	0 174	500 c c water
1/18	494	0 680	60 9	1 620	0 469	0 186	500 c c water
1/19	517	0 735	57 5	2 186	0 399	0 244	500 c c water
1/20	593	0 790	51 5	2 168	0 335	0 308	500 c c water

*Killed at 4 p m , January 20 Postoperative life 101 hours

The chlorids underwent also a temporary postoperative increase and this may account, in part, for the high K In subsequent days the chlorid percentage decreased to below normal, the nitrogen percentage increased tremendously

EXPERIMENT 3 (Dog 11) —Only one control day, March 20, was available in this experiment The operation was performed on March 22, at 11 a m Blood was drawn on March 23, 24, 25, 26 and 27 The animal appeared very weak and was killed on March 27, 12 noon, survived 121 hours The postoperative changes were identical with the previous results Specific gravity and Δ increased daily, the electrical conductivity did not show such a sharp postoperative rise as in the other two experiments, not reaching its maximum until the second day after operation It then fell gradually until death The viscosity was unchanged and the chlorids decreased as the nitrogen content increased

TABLE 3 —BILATERAL NEPHRECTOMY, EXPERIMENT 3 DOG 11 *

ite	Sp Gr 1 0—	Δ	$K_{20}10^{-4}$	Viscosity c c per sec	NaCl %	N %	Wgt kg	Remarks
20	682	0 590	32 4		0 635	0 089	12 88	Food and 500 c c water, operation Mar 22, 11 a m
23	650	0 680	34 6	2 578	0 455	0 161	12 98	Practically no food eaten given 500 c c water
24	666	0 735	39 0	5 440	0 443	0 215	12 85	Practically no food eaten given 500 c c water
25	675	0 805	35 5	2 860	0 422	0 215	12 55	Practically no food eaten given 500 c c water
26	700	0 825	31 4	3 190	0 359	0 311	12 32	Practically no food eaten given 500 c c water
27	720	0 925	30 0	3 092	0 276	0 363	12 15	Practically no food eaten given 500 c c water Blood drawn at 10 a m

*Killed 12 a m March 27 Postoperative life 121 hours

24 It is impossible to explain or discard this result since it happened that on this day the determinations were done in triplicate

II. DOUBLE URETERAL LIGATION

The plan of these three experiments was similar to that outlined for the double nephrectomy The control period was followed by the operation, after which blood was drawn daily until the death of the animal

EXPERIMENT 4 (Dog 3) —This animal survived fifty-nine to sixty nine hours Operation took place January 16, 11 a m A comparison of the results for the two postoperative days, January 17 and 18, with the three controls, January 11, 13 and 15 indicates that the specific gravity and Δ increased gradually until death, the electrical conductivity underwent a decided decrease after the operation, but on the second day had increased somewhat Little change occurred in the viscosity, if anything, a slight rise was in evidence The chlorids were also increased on the first postoperative day, but on the second had dropped below normal The nitrogen percentage was variable This experiment is somewhat atypical

TABLE 4 —DOUBLE URETERAL LIGATION EXPERIMENT 4 DOG 3*

Date	Sp Gr 1 0—	Δ	$K_{20}10^{-4}$	Viscosity c c per sec	NaCl %	N %	Wgt kg	Remarks
1/11	611	0 605	41 8					Food and 500 c c water
1/13	584	0 605	43 5	2 352	0 518	0 054		Food and 500 c c water
1/15	555	0 610	47 7	2 042	0 483	0 058		Food and 500 c c water
1/17	671	0 635	30 9	3 175	0 614	0 092		Operation Jan 16, 11 a m No food 500 c c water given
1/18	686	0 660	36 4	2 578	0 396	0 053		No food, 500 c c water given

*Death during night January 18-19 Postoperative life fifty-nine to sixty-nine hours

EXPERIMENT 5 (Dog 5) —This animal died on February 4, just after blood had been drawn for analysis Postoperative life, ninety-nine hours Two control days, January 27 and 31, were followed by four successive days, February 1, 2, 3 and 4, following the operation, February 1, 11 a m The results after operation agree in the main with the previous experiment The specific gravity and Δ show daily increases and the viscosity remains almost unchanged, except just before death when it rose very high The electrical conductivity followed the usual postoperative changes at first an increase and then a gradual decrease until death occurred The chlorids showed the usual postoperative daily decrease and the amount of nitrogen gradually became augmented

TABLE 5 —DOUBLE URETERAL LIGATION EXPERIMENT 5 DOG 5*

Date	Sp Gr 1 0—	Δ	$K_{20}10^{-4}$	Viscosity c c per sec	NaCl %	N %	Wgt kg	Remarks
1/27	602	0 660	39 7	2 800	0 516	0 102		Food and 500 c c water each day until operation
1/31		0 650	37 8		0 527			Food and 500 c c water
2/1	603	0 675	42 7	2 306	0 495	0 188		Operation Jan 31, 11 a m Food and 500 c c water
2/2	677	0 670	45 5	2 195	0 418	0 209		No food or water taken
2/3	695	0 720	40 7	2 404	0 430	0 274		No food or water taken
2/4	731	0 785	21 8	4 063	0 316	0 335		No food or water taken

*Death February 4, 2 p m Postoperative life ninety nine hours

Experiment 6 (Dog 13) —In this experiment there is only an incomplete analysis of one control, four days before operation, April 29, and one sample just previous to the operation The results for the two postoperative days agree entirely with the other experiments The operation was performed May 4, 11 a m The animal survived until the night of May 6-7, 59-69 hours The specific gravity, Δ and nitrogen percentage gradually increased, the chlorids decreased and the electrical conductivity showed the usual rise succeeded by a fall until death No viscosity determinations were made

Table 6 —Double Ureteral Ligation Experiment 6 Dog 13*

Date	Sp Gr 1 0—	Δ	$K_{20}10^{-4}$	Viscosity c c per sec	NaCl %	N %	Wgt kg	Remarks
4/29		0 615	34 3				16 30	Food and 500 c c water each day until operation
5/4	512	0 610	36 0		0 442	0 069	15 89	No food, 500 c c water given
5/5	562	0 685	51 4		0 441	0 178	15 87	Operation May 4, 11 a m No food, 500 c c water given
5/6	673	0 720	32 4		0 348	0 245	15 57	No food, 500 c c water given

*Death during night May 6-7 Postoperative life fifty-nine to sixty-nine hours

III EXAMINATION OF THE URINE FOLLOWING RELEASE OF LIGATURES AND THE ELIMINATION OF WATER, PURIN BASES AND URIC ACID INTO THE INTESTINE (FECES) DURING LIGATION AND NEPHRECTOMY

The difficulties associated with the accomplishment of a successful termination of an experiment of this type are myriad in number, and hence we are able to present but two, in one of which (Experiment 7, Dog 6), the ligatures were in position seventy-two hours and in the other (Experiment 8, Dog 8), 120 hours Autopsies in both instances revealed minute healed abscesses indicating that during the time of ligation an infection occurred which had not proceeded with sufficient rapidity to cause the death of the animal but which cleared up with the removal of the ligatures

The results of the control days as well as those subsequent to the release of ligatures and reimplantation are given in tabular form [25] It must be recalled that these animals before operation were placed on a low nitrogenous diet of 10 gm casein, 100 gm cracker-dust and 20 gm of lard As can be seen from the tables, the animals ate little or nothing during the time the ligatures were in place Some water was taken In all metabolic studies of this character there arises the uncontrollable factor of irregularity of food absorption due to loss of appetite and vomiting

25 The method of analysis employed was as follows Total nitrogen Kjeldahl, ammonia total and ethereal SO_3 Folin (ventilation at room-temperature with sodium carbonate) sodium chlorid Mohr phosphates uranium titration with potassium ferrocyanid

TABLE 7.—URINE, BEFORE LIGATION AND FOLLOWING IMPLANTATION OF URETERS. EXPERIMENT 7. DOG 6.

Date	Vol. in c.c.	Reaction to Litmus	Sp. gr. 1.0—	Total Nitrogen, gm.	NH_3-N, gm.	NH_3-N % to Tot. N	P_2O_5, gm.	NaCl, gm.	SO_3* in gms — Total	Inorg.	Ethereal	Δ	$K_{20}10^4$	Remarks
1/29	476	neutral	14	8.10	0.249	3.07	0.522	2.136	1.617	1.555	0.062	1.720		Note that this is a forty eight-hour period
1/30	Ligation both ureters, 11 a. m.													First specimen of urine obtained was not analyzed owing to blood and vomitus contamination
2/2	Implantation both ureters, 11 a. m.													
2/3	500	strong acid	10	4.30	0.055	1.27	0.359	0.696	2.520	2.030	0.490	0.965	66.4	Urine clear, no reduction, trace protein. Sediments contained a few epithelial cells, no casts
2/4	765	strong acid	13	9.31	0.028	0.30	0.582	0.551	2.888	1.885	1.003		65.3	
2/5	502	strong acid	15	6.81	0.058	0.85	0.489	0.320	1.908	1.368	0.540	1.205	66.6	Very little food eaten but 500 c.c. water daily. Still traces of protein, no reduction. Protein removed before analysis
2/6												0.960	60.8	
2/7														
2/8	590	strong acid	08	4.65	0.073	1.57	0.378	0.360		1.387		1.185 1.045	65.7 68.0	

*Calculated as $BaSO_4$

TABLE 8.—URINE, BEFORE LIGATION AND FOLLOWING IMPLANTATION OF URETERS EXPERIMENT 8 DOG 8

Date	Vol in c c	Reaction to Litmus	Sp gr 1 0—	Total Nitrogen, gm	NH_3-N, gm	NH_3-N% to Tot N	P_2O_5, gm	NaCl, gm	—— SO_3* in gms —— Total	Inorg	Ethereal	Water ingested in c c	Weight in kg	Remarks
2/13	192	strong acid	13	1 75	0 126	7 2	traces	0 252	0 818	0 763	0 055	50	5 36	
2/14	40	strong acid	37	1 73	0 102	5 9	traces	0 196	0 647	0 616	0 031	40	5 23	
2/15	35	strong acid	45	1 46	0 066	4 5	traces	0 190		0 601		25	5 30	
2/17	—— Ligation both ureters, 11 a m ——										16th—	30	5 35	Urine of the 23rd contained blood and was not analyzed
2/22	—— Implantation both ureters, 11 a m ——										17th—	180		
											22nd—	100	5 06	
											23rd—	150	4 90	
2/24	152	strong acid	19	2 11	0 071	3 4	traces	0 205	0 757			350	4 80	
2/25	61	strong acid	25	1 51	0 047	3 1	traces	0 182		0 451		200	4 78	
2/26	62	strong acid	20	1 31	0 053	4 0	traces	0 193				300	4 70	

*Calculated as $BaSO_4$

The figures of the urine analysis following reimplantation are somewhat difficult of accurate interpretation It would appear that the kidney very soon assumes its normal ability to eliminate water and inorganic salts It is true that the sodium chlorid figures in the tables show a decrease after the second operation, but in the light of evidence offered by the experiments in which the blood was examined during ligation, this decrease in sodium chlorid percentage of urine is to be explained most probably by the lowered content of this substance in the blood as the result of the ligation (see Experiments 4, 5 and 6) The phosphorus pentoxid output and the reaction indicate little, if any, change, the total sulphur trioxid in one experiment is increased in virtue of an increased output of ethereal sulphur trioxid and to a less extent also of inorganic sulphur trioxid The total nitrogen figures are very irregular and evidently depend on the amount of food taken during the ligation period This much may be said, however, that the total amount eliminated is much higher than could be accounted for by the nitrogen intake Unfortunately, we cannot produce figures as to the actual nitrogen balance, but it is evident that the figures for the output are in excess of what would be expected in the condition of practical fasting as it existed at the time We feel justified, therefore, in assuming that this excess represents nitrogen previously retained and now undergoing elimination In this connection it is interesting to note that both the absolute and percentile ammonia nitrogen are decreased Reasoning by analogy with the sodium chlorid, it would point to a decreased amount of this substance in the blood during ligation or to a diminished ability on the part of the kidney to eliminate it as the result of the operative procedure Unfortunately we possess no figures for the variation in the ammonia content of the blood during ligation

Attention should also be directed to the figures for the weight of the animal in relation to food and water ingestion (Experiment 8) During the five days of ligation the loss in weight amounted to 450 gm, and the intake of water and food aggregated 510 gm , no feces having been voided during this time, there occurred a loss of material via skin and lungs amounting to 960 gm It would appear that the lungs and skin as the remaining excretory pathways had attempted to assume vicariously the eliminative function of the kidney In how far this has been limited to water alone cannot be determined from the data obtained

EXAMINATION OF THE FECES

In Experiments 1 and 2 (Dogs 1 and 4, whose kidneys had been removed) the feces were collected before and after the operation From the table, it can be seen that apparently the organism does not employ the method of water excretion into the intestine in order to offset the loss of the renal function The water content of the feces is increased

only very slightly as the result of the nephrectomy In the case of ureteral ligation we can present only the figures for a normal dog and, in comparison, data which resulted from experiments on several animals during ligation The tables indicate that if anything, the percentage of moisture in the feces is diminished Further analysis of these various fractions of feces was carried out only with respect to the elimination of uric acid and purin bases These substances were chosen as examples of a possible vicarious elimination through the intestine The examination was made by the Kruger-Schmidt method In each instance, only traces of copper precipitate could be obtained and the results can be stated as negative Apparently, therefore, the purin bodies are not eliminated through the intestine and unless, therefore, they undergo further oxidation as the result of their retention, they must form part of the nitrogenous substances which are responsible for the gradual increase in non-coagulable nitrogen of the blood following either nephrectomy or ligation

TABLE 9 —FECES—BILATERAL NEPHRECTOMY, DOG 1

Normal			Following Operation		
Date	gm		Date	gm	
12/24	60		12/29	49	
12/25	100		12/31	71	
12/26	77		1/1	56	
12/27	17		1/2	15	
12/28	67			191	(moist)
	321	(moist)		73	(air-dry)
	137	(air-dry)		118=61 7%	water
	184=57 3%	water			

TABLE 10 —FECES—BILATERAL NEPHRECTOMY, DOG 4

Normal			After Operation		
Date	gm		Date	gm	
1/12	25		1/18	47	
1/13	12		1/19	25	
1/14	126			72	(moist)
	163	(moist)		22	(air-dry)
	87	(air-dry)		50=69 4%	water
	76=46 6%	water			

TABLE 11 —FECES—DOUBLE URETERAL LIGATION, DOGS 2, 5 AND 6

Normal Dog 2			After Operation Dogs 2, 5 and 6		
Date	gm		Date	gm	
12/24	35		1/8	13	
12/25	33		2/2	13	
12/26	25		2/3	13	
12/29	10		2/8	22	
12/30	18			73	(moist)
12/31	3			58	(air-dry)
1/2&3	25			15=20 5%	water
1/4	25				
1/5	22				
	196	(moist)			
	90	(air dry)			
	106=54 1%	water			

A consideration of the results obtained by previous investigators, and those presented in this paper, would serve to emphasize the fact that, so far as can be judged from the experimental evidence at present available, there exists no difference in the condition of the animal following bilateral *nephrectomy and double ureteral ligation* It is not correct to take the length of postoperative life of the animal as a criterion of the severity of the process or as indicative of differences in condition Too many other factors secondary to the surgical interference, but not the direct result of it, are more important in determining the life duration Thus the infection which we have observed in the early ligation experiments brings about changes tending to shorten the life of the animal Whether the presence of organisms in the blood of dogs, and their growth in localities which present a *locus minoris resistentiæ,* is widespread or not, needs further study The work of Hess[26] is suggestive in this connection, in that the results indicate a possible path by which infection might proceed, if bacteria can pass from blood into the intestine there exists no valid reason why passage could not occur in the opposite direction when the condition of the blood acted as a chemotactic stimulus on the organisms At present no connection can be drawn between this type of infection (streptococcus) and that found in dogs' livers removed aseptically from the body [27]

The results here detailed agree with those already reported, in that the molecular concentration of the blood increased after operation and until the time of death In an examination as to the causes which lead to this increase, it becomes evident from our results that the increase is not at the expense of retained sodium chlorid The gradual decrease in percentage of chlorids in each successive daily sample of blood points to a passage of these substances out of the blood, various paths are available If they enter the tissues, on account of an increased permeability of the endothelial lining, one would expect to find as a result an increased content of chlorid in the muscle and, perhaps, as concomitant an increased amount of water (edema) also Something of this sort does occur in the rabbit and edema appears as the result of surgical or toxic interference with renal function Strangely enough, however, edema never is present in dogs under similar conditions and at autopsy the subcutaneous and muscle tissues of dogs reported here seemed to be drier and to contain less water than usual [28] The chlorids may be excreted by the skin, but in dogs such a method is practically excluded, since dogs never sweat The last point of exit is the gastro-intestinal tract Excretion in this manner may be brought about either by the appearance of

26 Hess Proc Soc Exper Biol and Med, 1910, vii, 82

27 Jackson, H C Jour Exper Med, 1909, xi, 55

28 Experimental data bearing on these points will be presented in another paper

chlorin, as hydrochloric acid of the gastric juice, or as the result of the vicarious secretion of sodium chlorid by the cells of the intestinal mucosa This latter possibility receives additional support from the experiments of Salomon and Wallace,[29] who found sodium chlorid among the normal excretory substances of the intestine In view of the condition of the animal, and the fact that little or no food was ingested during the time when the chlorids were disappearing from the blood, it appears improbable that gastric juice was being secreted Hence, of these two possibilities, that of vicarious excretion seems most probable, although, unfortunately, we have no analytical results to substantiate it The urine which was obtained during the first days following the release of ligature of ureters adds additional proof to that obtained by blood analysis, i e, that the sodium chlorid content of the blood following both types of surgical procedure progressively diminishes to death This decrease, in all probability, forms the causative agent in bringing about the fact noted by so many observers, that the electrical conductivity and the molecular concentration hold no apparent relationship to each other In our experiments there exists, within certain limits, a well-defined parallelism between the chlorid content and the electrical conductivity, both of these factors after a postoperative rise[30] tending to decrease until death That the fall is not more pronounced may be explained by the fact that in the molecular increase in concentration which occurs, there is brought about an increase, in part, of substances with relatively large molecules which dissociate but slightly and, in part, of compounds which depress the dissociation of the inorganic salts With the data at hand, it is impossible to decide which factors are the most potent in bringing about the observed changes in the electrical conductivity The decrease in chlorids observed in these experiments might suggest an explanation On the other hand, Bugarszky and Tangl[5] consider that the chlorids play a rather small part (7 per cent) in the conductivity condition, as they exist in the blood, the carbonates being more important in this connection, in fact, a superficial examination of the blood would incline one to the belief that following the surgical procedure the carbonates are largely increased in the blood If this is true there must occur a large simultaneous increase of colloidal substances (proteins) which would offset the increase in ionizable compounds by their depressive power on dissociation

29 Salomon and Wallace Med Klinik 1909, v 579

30 It is interesting in this connection to note that Magnus (Arch f exper Path u Pharm, 1899 xlii, 250) was able to produce edema in dogs only as the result of salt infusion, from twenty-four to forty-eight hours, following complete nephrectomy or ureteral ligation This might indicate of course a temporary derangement of water and salt equilibrium between blood and tissues, brought about by an altered permeability of the endothelial cells of the capillaries The temporary increase in chlorids noted in these experiments could be construed as part of the process

Apparently, the sulphates and phosphates do not leave the blood in a way similar to the chlorids, and they may also add their part in tending to diminish the decrease in K The chemical analysis together with the results for the specific gravity and Δ, all point to an increased concentration of the blood, this is the reverse of what occurs in nephrectomized rabbits in which a hydremia is followed by an edematous condition As previously stated, this latter state of affairs does not occur in the dog Apparently there exists no relationship between the amount of water ingested and the progressive increase in molecular concentration of the blood If more water is ingested, a corresponding amount is eliminated via the lungs Our results with the feces do not indicate that this water is removed in this way This accords with the negative results obtained in attempts to prolong the life of operated animals by salt (water) infusion[9] Only temporary variations in the blood result, and just as in the normal animal, following similar procedures, the blood with astounding rapidity assumes its normal level,[31] so the blood of these animals which have been operated on quickly reassumes the same abnormal condition as before All of this indicates that the unknown mechanism which regulates the exchange of water between intake, through the intestinal capillaries, and output, via capillaries of lungs, skin, kidney and intestine, has become disturbed and that the equilibrium is day by day reaching higher levels of concentration Until it becomes possible to explain this regulative mechanism, we cannot expect by this means to prolong, to any great extent, the life of the operated animal

This increased molecular concentration is in itself not to be considered as the cause of death Undoubtedly, the tremendous increase of non-coagulable nitrogen is indicative of an increase in substances formed in the endogenous metabolism of the cell and toxic to the organism The presence of these compounds in excessive amount in the blood and cells must act as the causative factor in the death of the animal That ammonium salts probably do not form a part of the nitrogenous increase can be reasoned from the fact that when the ureters are reimplanted the ammonium content of the urine secreted at that time is very low Of course, it could be argued with equal force, perhaps, that the existing pathological conditions in the convoluted tubules were of a character to retain ammonium salts, even though apparently other nitrogenous compounds were not simultaneously withheld

There exists a lack of evidence that these animals die with symptoms similar to those of uremia in man They become lethargic but not comatose, convulsions are rarely present There is no indication of increased reflexes, of gastro-intestinal symptoms, vomiting is the only one constantly present From the standpoint of the superficial examination

31 Sollmann Arch f exper Path u Pharm, 1901, xlvi, 1

of the blood, the most marked feature was its intense venosity and accompanying increased viscosity The blood, as it flowed out of a vein just before death, was of a character closely resembling molasses It became almost impossible to draw the blood into the large hypodermic needle ordinarily employed Coagulation occurred less rapidly and the amount of the clot was decidedly augmented Meltzer and Salant[32] report delayed clotting in nephrectomized rabbits

In experiments of the kind described in this paper, no single individual factor thus far examined throws sufficient light on the question to bring about complete elucidation If, however, one considers the changes in physico-chemical constants occurring as the result of the surgical interference, and correlates these with the superficial examination of the blood and general condition of the animal, it becomes evident that the cause of death is brought about by the interaction of a variety of altered chemical processes

In all probability, the general condition is a toxemia either initiated by, or resulting in, a gradual asphyxia These two factors form a vicious cycle Accumulated products of normal cellular catabolism, non-toxic in themselves, among which carbon dioxid may form an important member, cause the appearance in the cells and tissues of incompletely oxidized products further aggravating the asphyxial condition The large carbon dioxid content of the blood augments the viscosity and hence renders more difficult the passage of the blood through the capillaries The slowed capillary rate in turn diminishes the oxygen supply to the tissues and the removal of carbon dioxid is hindered

SUMMARY

1 When all the various conditions of the experiment (diet, lack of infection, etc) remained constant, there appeared to be a slight tendency on the part of the animals with both kidneys removed to survive the operation for a longer period than was the case in double ureteral ligation The analysis of the blood following both operative procedures showed no differences which could account for this

2 The molecular concentration (Δ) of the blood increased after both operations until death The electrical conductivity (K) and chlorid content of the blood, after a temporary rise on the day following the operation, progressively decreased Hence, the rise in concentration was brought about by an increase in organic substances mainly nitrogenous and non-coagulable in character, as was shown by the blood analysis

3 Following both operations, the blood becomes more venous with a resulting increased viscosity due to carbon dioxid and the time of coagulation is increased

32 Meltzer and Salant Jour Med Research 1904, xii, 63

4 No vicarious elimination of water, uric acid or purin bases occurs into the intestine

5 The urine secreted after the reimplantation into the bladder of the ligated ureters was of a character which did not indicate great renal changes The variations might be explained by the altered condition of the blood and tissues The secretion was somewhat low in chlorids on account of low content of chlorids in the blood at that time, high in total nitrogen but low in ammonia nitrogen The sulphates showed an irregularity which might be construed as pointing to cellular dyspnea

6 Hydremia does not occur as the result of either operative procedure, and no evidence of edema was ever present In fact the tissues at autopsy appeared drier than the normal

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LEVULOSURIA

WITH A REPORT OF AN UNUSUAL CASE *

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The rarity of the condition of levulosuria unassociated with glycosuria justifies a detailed report of the case which we were able to study The subject may be conveniently discussed under three headings

1 Alimentary levulosuria in diseases of the liver

2 Levulose associated with glucose in diabetes mellitus

3 Rare cases in which levulose alone has been found

As our case belongs to the last division, the first two conditions will be discussed only as they may throw light on the clinical features and pathogenesis of levulosuria, and the extensive literature on the subject, recently reviewed by Koenigsfeld,[1] will be handled in the same manner In patients suffering from certain diseases of the liver, H Strauss[2] found that the feeding of 100 gm of levulose produced levulosuria, and this has been extensively used as a method of functional diagnosis of liver disease It has been supposed that in functional hepatic disturbances the liver is unable to convert levulose into glycogen, and levulose fed by mouth is consequently passed unused Experimental work of Sachs[3] and others tends to support the view that hepatic insufficiency may be associated with alimentary levulosuria, since they found that in dehepatized frogs levulosuria can be easily produced by injecting or feeding levulose The muscles of such frogs contained no levulose Glucose, however, given to dehepatized frogs does not produce glycosuria, and correspondingly the muscles of these frogs contain an increased amount of glucose

The presence of levulose along with glucose in diabetic urine is not very common, but there seems to be quite a diversity of opinion as to its incidence In 1,000 cases of diabetes, Seegen[4] found no levulose, in nineteen cases, Schwarz[5] found six with levulose, von Noorden[6] claims to have found it only rarely in mild cases, but almost always in severe cases, and he considers its presence an unfavorable prognostic sign In

*From the laboratories of the Michael Reese Hospital, Chicago

1 Koenigsfeld Ztschr f klin Med, 1909 lxix, 291

2 Strauss Deutsch med Wchnschr, 1901, xxvii, 757

3 Sachs Ztschr f klin Med, 1899, xxxviii 87

4 Seegen Centralbl f d med Wissensch, 1884, xxii 753

5 Schwarz Deutsch Arch f klin Med 1903 lxxvi, 233

6 von Noorden Die Zuckerkrankheit Berlin, 1901

von Mering and Minkowski's original work on pancreatic diabetes, tolerance for levulose was not disturbed, and von Noorden considers that within certain limits levulose tolerance in diabetes is not changed When levulose appears, then, in diabetes it is an indication of severe disturbance of carbohydrate metabolism

There are, on the other hand, cases of mixed melituria not like true diabetes Lion's[7] case showed levulosuria and glycosuria, the former being affected by levulose in the diet, the latter by glucose May's[8] case of transverse myelitis showed the undoubted presence of both glucose and levulose in an alkaline urine The feeding of levulose, glucose, or saccharose had no influence on the sugar output, although the removal of all carbohydrate from the diet resulted in the disappearance of sugar It is very possible that the levulose here was formed from dextrose, by conversion by the alkaline urine in bladder According to the work of the chemists Lobry de Bruyn and Alberda von Ekenstein,[9] a solution of glucose in alkaline media is partially converted into levulose and other allied hexoses, and only recently Koenigsfeld[1] reported a case of true diabetes in which levulosuria developed following the exhibition of alkaline mineral waters Koenigsfeld further gave dextrose by mouth during a sugar-free period and thereby produced glycosuria, but when the dextrose was preceded and followed by alkaline mineral waters and the urine became alkaline, levulose appeared Levulose given by mouth in Koenigsfeld's case caused no changes in the urine, showing that the levulosuria was not due to lowered tolerance for levulose Possibly von Moraczewski's[10] cases of levulosuria associated with alkaline urine might be classed under this head, for here, although diminished tolerance for levulose undoubtedly existed, glucose also increased the levulosuria when the urine was alkaline in reaction His cases, however, were incompletely studied, and it is rather difficult to recognize from his reports the exact origin of the levulose That "urinogenic levulosuria"—as Koenigsfeld calls this type of conversion of dextrose into levulose in the urinary bladder—can exist and can be the cause of levorotation in diabetic urines must be considered proved

Only six cases of pure levulosuria have been reported in the literature Seegen's[4] first case, carefully analyzed later by Kulz,[11] seems to have been one of pure levulosuria Rosin's,[12] Schlesinger's,[13] and Neubauer's[14]

7 Lion Munchen med Wchnschr, 1903, l, 1105
8 May Deutsch Arch f klin Med, 1896, lvii, 279
9 De Bruyn, Lobry and von Ekenstein, Alberda Ber d Deutsch chem Gesellsch, 1895, xxx, 3078
10 von Moraczewski Ztschr f klin Med, 1907, lxiv, 503
11 Kulz Ztschr f Biol, 1890, xxvii, 228
12 Rosin Salkowski Festschrift, 1904, p 105, Rosin and Laband Ztschr f klin Med, 1902, xlvii, 182
13 Schlesinger Arch f exper Path u Pharm, 1903, l, 272
14 Neubauer Munchen med Wchnschr, 1905, lii, 1525

patients had symptoms of diabetes, Lépine and Boulud's[15] developed during puerperium, and Schwaiz's[5] had endocarditis Jolle's[16] two cases cannot be accepted, nor can Marie and Robinson's,[17] as not sufficient evidence is given to prove the presence of levulose alone

Rosin's case differs from all the others in that the excretion of levulose had no relation to carbohydrate intake, and levulose by mouth had no effect In this case levulosemia was demonstrated even when the patient was not passing levulose The disturbance of metabolism in this case cannot be stated In all the others the levulosuria was surely an indication of diminished tolerance for levulose, for in them a direct relationship between intake and excretion was shown This, interestingly enough, was shown only in regard to levulose or higher carbohydrates which, on splitting, form levulose Except, then, for Rosin's case, the other reported cases show an intolerance for levulose identical with the intolerance for glucose in a mild diabetes Neubauer, who was able to study his patient in a more complete manner than any of the previous writers, in testing the assimilation limit of his patient for levulose, found that no matter how small an amount was given (at least down to 3 8 gm) always a constant portion, between 15 and 17 per cent, was excreted

The case we have to report is almost identical in its urinary findings with Neubauer's, but it has a special interest in that clinically it presents phases indicating marked disturbance of the internal secretions The relation of these glands to carbohydrate metabolism is a subject of vast interest, beyond the scope of this paper, but it is at least an unusual coincidence to find in the same patient such marked variation from normal carbohydrate metabolism associated with such discord in the usual harmonious relations of these glands

The patient is reported from the service of Dr D'Orsay Hecht, at the Michael Reese Hospital, to whom we are indebted for the clinical notes As the clinical aspects will be reported in detail,[18] we shall give only an outline

Patient—A male, aged 16, a Russian Jew, came to this country four years ago Two years ago, at the beginning of puberty, he noticed a tremor of the right arm and hand, recently the tremor has been noticed in the left arm, and in the head No other symptoms have been complained of, and all symptoms referable to diabetes were negative The family history was likewise negative

Examination—The boy, 5 feet, 8¾ inches tall wears a No 9 glove, No 8 shoe and No 7½ hat There is a marked cyanosis of the hands feet, nose and ears, a marked tremor of both arms and hands, and of the head The pelvis is distinctly of the female type, the testes are unusually small, the penis large, the hair development normal, except for unusual thickness on the head The blood shows a slight secondary anemia a leukocytosis varying between 10,000 and

15 Lépine and Boulud Rev de méd 1904, xxiv, 185
16 Jolles Arch d Pharm 1906, ccxliv 542
17 Marie and Robinson Semaine med, 1897 xvii 250
18 Journal of Nervous and Mental Diseases

25,000, with a normal differential count, blood pressure was around 110 Stool examinations made several times were negative The urine, which will be discussed in detail later, showed a surprising constancy in its findings The average amount was 1,500 to 2,000, specific gravity of 1,022, and it contained albumin and casts, indican and levulose Frequently, but *not always*, the urine was alkaline and contained an abundance of triple phosphate crystals Acetone and diacetic acid were constantly absent Frequent ammonia and nitrogen estimations on various diets gave no abnormal figures Bile was never present and urobilinogen (dimethylaminobenzaldehyd test) was not increased

The findings in the urine of a reducing body which gave an atypical delayed reaction with Fehling's solution and reduced Nylander's, but was levorotatory, immediately suggested the presence of levulose, and was followed by detailed study of the nature of the reducing body

Diagnosis—Before a diagnosis of pure levulosuria is justified, the following conditions must be fulfilled

1 Reduction of metallic salts (Fehling's and Nylander's)
2 Levorotation
3 Fermentation into alcohol and carbon dioxid with complete disappearance of the reducing and rotatory substance
4 Osazone crystals, with melting point 204 6°
5 A positive Seliwanoff reaction
6 The figure for rotation figured as dextrose must bear a constant relation to the figure from copper reduction (0 57 to 0 924)

With the patient on an ordinary ward diet, containing carbohydrates, these conditions were constantly fulfilled The Seliwanoff reaction was intensely positive, and the urine was fermented by yeast, showing carbon dioxid and alcohol After twenty-four hours' fermentation there was often still present a levorotatory substance, which, however, completely disappeared in forty-eight hours With phenyl hydrazin an osazone was formed exactly like glucosazone In all the work a comparison of the readings made by the Benedict copper-reduction method, and by the polariscope, showed that we were dealing with one substance and not with a mixture of levulose and glucose

TABLE 1—EFFECT OF WARD DIET *

Date	Quantity	Time of Specimen, Hrs	Fehling	Seliwanoff	Polariscopic % as levulose	Polari gm	Benedict % as levulose	Nitrogen	Ammonia
2/22	960	24	+	+	0 51	4 89	0 65	10	
2/23	1,370	24	++	++	0 34	4 55	0 31	13	0 88
2/28	1,020	24	++	++	0 8	8 16	0 98		
3/ 1	1,700	24	+++	+++	0 8	12 6	0 96	15	2 34
3/ 2	1,250	24	++	+	0 17	2 12		11	0 9
3/ 3	1,500	24	++	+	0 28	4 28		15	1 3

TABLE 2—EFFECT OF CARBOHYDRATE-FREE DIET *

3/ 8	1,350	24	0	0	0	0	0		
3/ 9	1,340	24	0	0	0	0	0	13	0 5
3/10	1,250	24	0	0	0	0	0	18	1 5

* Figures for Benedict are too high, owing to an error in standardization of solutions

Some discussion is necessary here as to the technic of the various tests The Seliwanoff test has been criticized and modified by every worker, and

recently Borchardt[19] has attempted to systematize its use by his own modification This, like all the other modifications, when carefully guarded is about as accurate as the original The test is based on the principle that levulose in the presence of hydrochloric acid and resorcin will produce a deep-red color, soon changing into a red precipitate While the test is very delicate for levulose, it is given also by nitrites, and by glucose in concentrated solution, consequently it cannot be considered a scientifically accurate test For practical purposes, however, the original test serves as usefully as does any of its modifications for the detection of levulose, even in the presence of glucose Working with pure solutions of the sugars in water, we obtained the best results by using equal parts of concentrated hydrochloric acid and of sugar solution, to which is added a knife-point of resorcin, and heating in a boiling water-bath Even minute amounts of levulose give an intense reaction with this technic inside of thirty seconds, whereas glucose under 2 per cent takes four minutes, and a 4 per cent solution, two minutes By this means we have detected numerous times levulose in our case, even when the urine did not reduce Fehling's solution If, then, one wanted to search for levulose in the presence of even a large amount of glucose, the urine could be diluted, and heated over a water-bath for thirty seconds The chance of confusion from nitrites can be avoided by employing fresh urines

The study of fermentation also brought out the fact that stale, ammoniacal urine might not ferment, even though there was definite evidence of the presence of sugar This was especially true with certain brands of commercial yeast, and was probably due to the alkaline reaction of the urine The orcein pentose test and the phloroglucin glycuronate tests were extensively done, the orcein never being positive, while the phloroglucin at times was positive when the levulose content of the urine was high Control tests, however showed that levulose by itself would give the phloroglucin test

Having established the identity of the reducing body as levulose, and having shown the absence of other reducing substances in the urine, we next attempted to decide into which group of levulosurias our case belonged Koenigsfeld's "urinogenous" type could be excluded, since levulose was present even when the urine was acid On an ordinary ward diet, containing as much carbohydrate as the patient wished to eat — and he was very fond of sweets of all kinds — the daily curve of levulose excretion was charted This showed a very small amount, or even absence of levulose in the early morning, a rise toward noon or 3 p m and then a fall — corresponding with what is found in mild cases of diabetes The removal of carbohydrates from the diet was followed by the immediate disappearance of sugar from the urine Later however after the patient

19 Borchardt Ztschr f physiol Chem 1908 lv 241

had been out of the hospital for about three weeks, there was still a slight trace of levulose present in the urine with the patient on a carbohydrate-free diet This was manifested only after eating

TABLE 3—DAILY CURVE OF EXCRETION ON UNRESTRICTED DIET

Date	Quantity	Time	Fehling	Seliwanoff	Levulose %	
					Polarise	Benedict
2/24		9 a m	0	0	0	0
2/24		12 m	++	+		0
2/24	100	3 p m	+++	+++	1 8	1 8
2/25		9 a m	0	0	0	
2/25		12 m	+	+	0 06	
2/25		3 p m	++	++++	1 3	
3/ 3	130	9 a m	+++	+++	0 8	0 72
3/ 3	120	12 m	+++	+++	1 48	1 5
3/ 3	120	3 p m	+++	+++	0 68	
3/ 3	120	6 p m	+	+	0 48	
3 /3	1,260	p m	0	0	0	
3/28	90	9 a m	+	+	0 11	
3/28	170	12 m	+	+	0 1	
3/28	210	3 p m	0	0	0	
3/28	240	5 p m	++	++	0 85	0 83
3/28	1,140	p m	+	+	0 4	

P M includes urine voided between 6 p m and 6 a m

TABLE 4—EFFECT OF FEEDING LEVULOSE ON FULL DIET

Date	Time, Hours	Levulose	Quantity	Fehling	Seliwanoff	Polarise Levulose, %	Polarise Levulose, gm	% Levulose Excreted
3/ 3	24	0	1,750	+	+		4 21	
3/ 4	24	100	1,720	+	++		14 34	10
3/ 5	24	0	1,500	+	+		4 12	
3/ 6	24	90	2,220	+	++		11 46	8
3/ 7	24	180	1,770	+	+		21 27	9

TABLE 5—EFFECT OF FEEDING LEVULOSE ON CARBOHYDRATE-FREE DIET AND ON EMPTY STOMACH

4/ 7	a m		1,320	0	0	0	0	
4/ 7	9 00	50						
4/ 7	12 00		240	+	++	1 89	4 56	9
4/ 7	2 30		240	0	0	0		
4/ 7	5 30		300	0	0	0		
4/ 8	a m		?	0	0	0		
	9 00	25						
	11 00		120	+	+	1 71	2 05	8 2
4/11	7 00		?	0	0	0		
	8 00	10						
	10 30		120	+	++	0 63	0 76	7 6

Levulose feeding was divided into two stages Various amounts were added to the ordinary diet, with a constant increase in the levulose output Based on the average for days before and after this experiment, it would seem that from 8 to 10 per cent of the amount taken in was passed

When feeding levulose on an empty stomach in amounts varying from 10 to 100 gm at one dose, the same approximate percentage was found in the urine It will be remembered that in Neubauer's case the unused levulose varied from 15 to 17 per cent, and this proportion was constant for any dose ingested

Glucose likewise was given both with the ordinary ward diet and on a fasting stomach, and in neither case did it affect the output of levulose or produce glycosuria When 100 gm were fed on an empty stomach, a trace of levulose could be found in the urine three to six hours afterward In the last experiment the control day, with the same diet minus glucose, showed the same trace of levulose, so that it seems warrantable to conclude that levulose was not made from glucose And since at no time did 100 gm of glucose produce glycosuria, there was undoubtedly complete tolerance for glucose

TABLE 6—EFFECT OF GLUCOSE PATIENT ON FULL WARD-DIET

Date	Glucose	Quantity	Fehling	Selwanoff	Polarisc Levulose, %	Polarisc Levulose, gm
3/11	100	1,600	+	+	0 46	7 36
3/12		2,000	±	+	0 23	4 6
3/13		1,800	0	+	0 11	1 98
3/15		1,575	+	++	0 63	9 9
3/16	100	1,675	+	+	0 23	3 85
3/17		2,190	+	+	0 34	7 4

Although two attempts to demonstrate levulosemia by the method of Rosin were unsuccessful, it seems reasonable to suppose that the negative results were due to technical difficulties and that levulosemia actually existed Rosin demonstrated levulose in the blood of his patient even when there was no levulosuria, and Neuberg and Strauss[20] proved its presence in the serum of a patient suffering with syphilis of the liver who had been given 100 gm levulose as a functional test

A priori, one might expect phlorizin injections to produce both glycosuria and levulosuria, but Schlesinger found that his patient with pure levulosuria reacted to phlorizin injection with glycosuria, while Neubauer's case of mixed melituria responded by showing both glucose and levulose in the urine In our patient the experiment was performed under various conditions On two different occasions 0 005 gm of

20 Neuberg and Strauss Ztschr f physiol Chem 1902 xxxvi 227

phlorizin were injected subcutaneously, with the patient on a mixed diet, and passing levulose in the urine The urine voided two hours after the first injection contained by copper sulphate reduction 0 53 per cent sugar (calculated as dextrose), and did *not* rotate the plane of polarized light, but gave a marked positive Seliwanoff reaction, thus showing that both glucose and levulose were present Therefore, calculating on the basis of a comparison of the specific rotations of dextrose and levulose, with their specific reductions of copper sulphate, this urine contained 0 2 per cent dextrose and 0 35 per cent levulose After the second injection the urine showed 0 3 per cent levorotation in a tube 189 4 mm long, and 0 66 per cent (as dextrose) by the Benedict copper-reduction, and, therefore, contained 0 21 per cent dextrose and 0 49 per cent levulose In neither case was the amount of levulose increased over what might have been expected for that hour of the day, and in both instances an undoubted glycosuria was produced A third intramuscular dose of 0 02 gm , given when the patient was on a carbohydrate-free diet and, therefore, showing no levulose in the urine, gave dextrorotation of 1 2 per cent, copper reduction to the same amount, and a negative Seliwanoff The summary of these experiments would be that, as in the normal individual, a pure glycosuria was caused by all injections The injections, made at a time when levulose was present in the urine, did not seem to increase the levulose, and the third injection, given during a levulose-free period, produced only glycosuria

TABLE 7 —EFFECT OF PHLORIZIN INJECTIONS WITH UNRESTRICTED DIET

Date	Time	Phlorizin	Quantity	Fehling	Seliwanoff	Dextrose, %		Levulose, %	Dextrose, %
						Polarise	Benedict.		
3/23	a m		1,230	+	+	0 4		0 23	
3/23	10 00	0 005							
3/23	12 00		240	+++	+	0	0 53	0 35	0 20
3/23	3 00		220	0	+	0 4		0 23	
3/31	10 30		90	0	±	0			
3/31		0 005							
3/31	11 30		60	+++	+	— 3	0 66	0 49	0 21
3/31	12 30		45	++	+++	—1	0 72	0 6	0 17
3/31	1 30		120	0	+	— 1			

TABLE 8 —EFFECT OF PHLORIZIN INJECTIONS WITH CARBOHYDRATE-FREE DIET

5/ 5	4 00			0	0	0			
5/ 5	5 00	0 02							
5/ 5	7 00			+++	0	1 2	1 2	0	1 2
5/ 5	7 00								

As has been stated, the clinical manifestations of this case were so suggestive of disturbances of internal secretions that several empiric

experiments were performed, in the hope of correlating the disturbance of carbohydrate metabolism with perverted activity of adrenal, thyroid and hypophysis Two injections of 0 6 c c epinephrin (adrenalin) 1 1,000, and a course of thyroid tablets, 1 gm a day, for six days, were without effect Pituitary tablets (Armour), 0 6 gm a day, for nine days, produced an apparent diuresis without an increase in the levulose output Of course, a series of observations like these cannot be accepted as excluding the possible interrelation of one or more of the glands of internal secretion with the levulosuria

SUMMARY

Our case of levulosuria belongs to the rare class of spontaneous alimentary levulosurias in which the levulose is derived only from ingested levulose or higher carbohydrates splitting off levulose Glucose has no effect on the excretion of levulose, nor is there any diminished tolerance for glucose The appearance of levulose in the urine is probably due to a partial inability to convert levulose into glycogen, which, according to present conceptions, is a hepatic function Consequently a constant proportion of levulose in the diet is excreted as such The disturbances in the nervous system and in the secondary sexual characteristics point to a disturbance of function of one or more of the ductless glands This perversion may be the etiologic factor in hepatic insufficiency (see von Noorden[21])

Recent work of Goetch, Cushing and Jacobson[22] showed that in dyspituitarism tolerance for levulose was on the same level as for dextrose, and it is possible that in our case the levulosuria may be merely a symptom in an obscure syndrome, involving as yet unsettled questions of disturbances in the ductless glands

3914 Ellis Avenue—4801 Indiana Avenue

21 von Noorden Med Klin, 1911, vii, 1

22 Goetch Cushing and Jacobson Bull Johns Hopkins Hosp 1911 xxii, 165

SOME OBSERVATIONS ON THE BLOOD-PRESSURE-RAISING SUBSTANCE OF THE ADRENALS IN ACUTE ADRENAL INSUFFICIENCY *

JEAN V COOKE, M D
NEW ORLEANS

By acute adrenal insufficiency is usually meant that group of cases in which, after a short fatal illness accompanied sometimes by severe gastrointestinal symptoms, sometimes by acute symptoms referable to the central nervous system, and sometimes merely by profound asthenia, or some combination of these, there is found at autopsy no adequate cause for death except some destructive process in the adrenal glands The cases are distinguished from Addison's disease by their short course and by the absence of pigmentation At autopsy the lesion is usually a thrombosis of the adrenal veins with hemorrhage into the medulla, but cases have also been noted of an acute inflammatory process, carcinoma, sarcoma or tuberculosis, involving the adrenal glands Those cases of adrenal hemorrhage occurring in infants and, as is thought by many observers, resulting in some way from an acute infection, may also belong to this group As to whether symptoms referable to an insufficiency of the adrenals can be recognized in the course of acute infectious fevers — a view championed especially by Sergent and other French clinicians — it is not the province of this paper to discuss, nor shall I detail the clinical symptoms that have been described in connection with the cases of acute adrenal insufficiency which have been reported It is sufficient to remark that the cases may present any of the symptoms that accompany Addison's disease except the pigmentation, and that the symptoms are usually severe A collection of cases was made by Lavenson[1] in 1908, and Sergent[2] has critically discussed the subject

REPORT OF CASE

The patient whose case I wish to report was admitted to the Pennsylvania Hospital Feb 4, 1911, in the service of Dr A V Meigs, to whom I am indebted for the notes on the clinical history

History —The patient was an Austrian, 40 years of age, with delirium and muscular twitchings The history obtained was very meager on account of his

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*From the Ayer Clinical Laboratory of the Pennsylvania Hospital, Philadelphia, and the Department of Research Medicine of the University of Pennsylvania

1 Lavenson, R S THE ARCHIVES INT MED, 1908, II, 62

2 Sergent Rev mens de méd int et de thérap, 1909, I, 801

mental condition and the fact that he spoke no English He had always been well until two days before admission, when, following excessive indulgence in oysters and whisky, he became ill

Examination—On admission, examination revealed a muscular, well-nourished man with expressionless face and staring eyes The muscles of his face, arms and hands were continually twitching and he continually muttered sentences that an interpreter said referred to obscene things Both pupils were moderately dilated and equal The breathing was jerky and spasmodic Physical examination was otherwise negative

Course—During the three days following, the patient was noisy and apparently irrational He passed urine and feces involuntarily The blood pressure was unfortunately not taken The temperature ranged from 99 to 101 8, averaging about 100, and the pulse varied between 86 and 136 The urine showed a moderate cloud of albumin, but no casts Three days after admission the pulse became very weak and rapid, the face cyanotic and the patient died

Autopsy was performed one-half hour post mortem, and the following is an abstract of the autopsy protocol (A 1416)

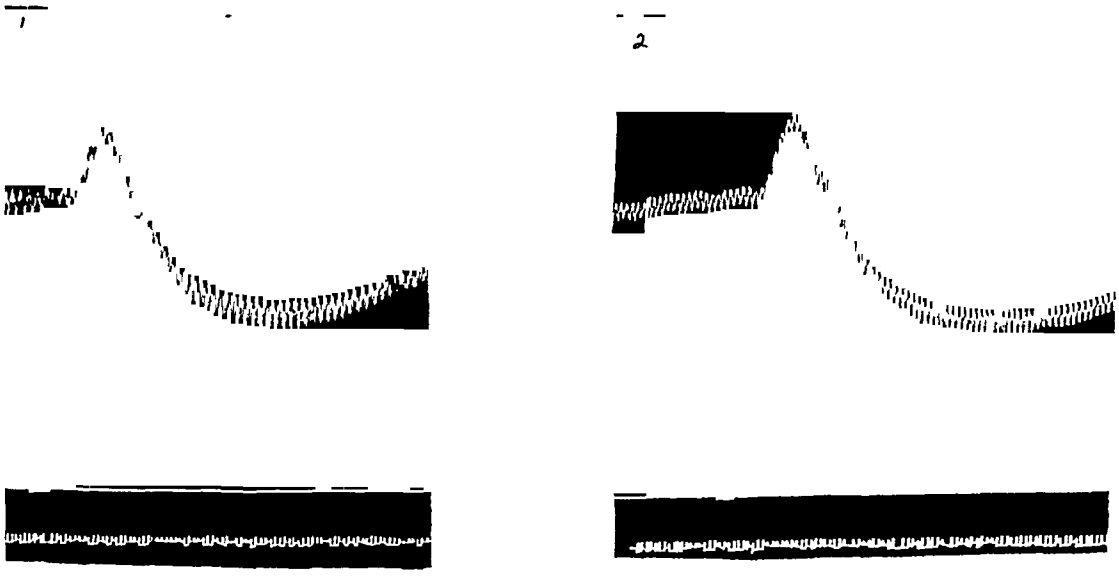

Fig 1—Injection of 1 minim of epinephrin solution (1-1000) In this and all following tracings, the upper line is the blood-pressure, the middle line is the signal and the lower line is the time in seconds All injections of tissue extracts were 2 c c of an extraction with ten volumes of normal salt solution

Fig 2—Injection of extract of normal-appearing portion of right adrenal

MACROSCOPICAL POST-MORTEM EXAMINATION

The body is that of a large, well nourished man 171 cm in length There is no rigor mortis There is slight post-mortem discoloration of the back neck and head, but no abnormal pigmentation of the skin and mucous membranes There is no edema of the extremities

Abdominal Cavity—There is a well marked panniculus adiposus and the serous surfaces are everywhere smooth and glistening The appendix is converted into a fibrous cord

Thorax—Both lungs are firmly bound to the chest wall by fibrous adhesions The left lung is everywhere crepitant and on section the cut surfaces are pale and appear normal At the apex is a firm scar The bronchial lymph nodes are small and pigmented black The right lung shows some irregular patches of bronchopneumonia in the lower lobe otherwise it is crepitant and pale and dry on section The bronchial lymph-nodes are small

Pericardium—The pericardium is smooth and contains no excess of fluid

Heart—The heart weighs 300 gm The cavities and valves and coronary arteries appear normal The myocardium is firm and pale brown in color

Spleen—The spleen weighs 190 gm and shows no gross lesions

Liver—The liver weighs 1 250 gm and measures 24 by 16 by 6 5 cm The capsule is smooth and rather dark brown in color Scattered beneath the capsule there are rather numerous small, light gray rather opaque areas, about 1 mm in diameter On section the liver is rather pale reddish brown in color, and scattered through the parenchyma there are numerous small gray, semi-translucent areas, about 1 mm in size

Kidneys—The kidneys weigh 300 gm and show nothing abnormal

Adrenals—The right adrenal is much enlarged and weighs 17 5 gm It has approximately the same shape as the normal adrenal but is quite firm and rubbery The surface is rather opaque and light yellow in color At the superior portion it has a normal appearance and the normal appearing portion weighs approximately 2 5 gm The remainder of the gland is firm and section is made easily The cut surface presents a smooth, uniform, rather firm, very pale yellowish appearance and is sharply marked off from the normal-looking adrenal, which occupies the superior extremity of the gland The left capsule, when dissected

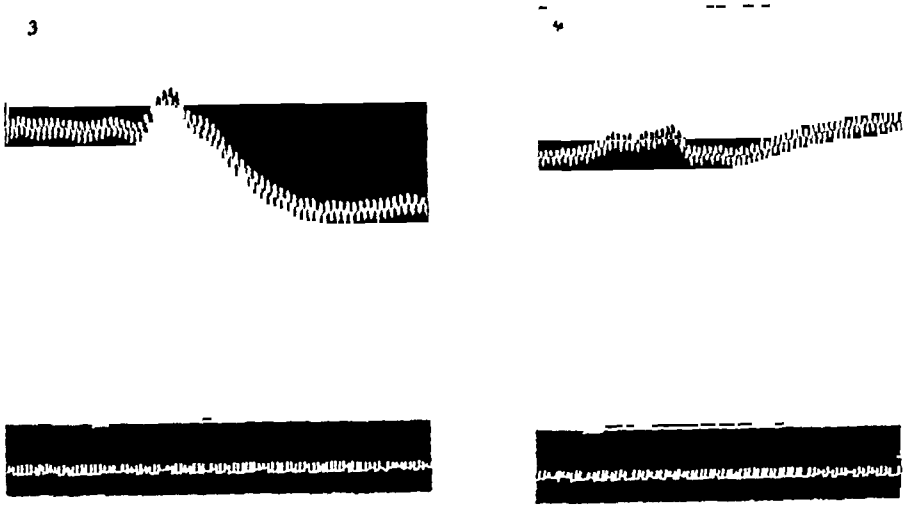

Fig 3—Injection of extract of left adrenal
Fig 4—Injection of extract of tuberculous portion of right adrenal

free from the surrounding fat, weighs 0 8 gm About one half of this gland consists of what appears to be a fibrous tissue, which on section is quite firm and in one place is seen to be a somewhat softened caseous appearing area about 2 mm in diameter The remainder of the gland is about 4 mm in thickness and on section shows a light yellowish brown tissue which has only a slight resemblance to the adrenal tissue

Urinary bladder, prostate, stomach, intestines, pancreas, larynx, pharynx and trachea appear normal

Thyroid Gland—This is of moderate size and on section is reddish brown One large normal appearing parathyroid is found on either side

Aorta—The aorta is smooth, elastic and shows a slight yellowish flecking of the intima

Brain—There is a congestion of the pial vessels and the pia is distended with clear fluid The cortex is in no place opaque and the meninges at the base and over the cortex appear normal The lateral ventricles are slightly dilated and filled with clear fluid No gross lesions are found on section of the brain substance

MICROSCOPICAL EXAMINATION

Sections of the heart, spleen, kidney, pancreas, thyroid, parathyroids and pituitary body show nothing unusual The lung shows some small areas of broncho-pneumonia In the liver the small opaque areas are epithelioid tubercles, some of which show a slight central caseation

Adrenals—The right adrenal shows an extensive caseous tuberculosis There is in the large yellowish portion of the right adrenal an extensive destruction of the gland, only a few cells of the zona glomerulosa being left Around the pink-staining caseous tissue there are seen epithelioid and lymphoid cells and an occasional giant cell Toward the superior pole the destruction is less extensive, and here are seen normal-appearing medullary and cortical tissue

Left adrenal That portion of the gland which grossly appeared fibrous shows a caseous area in the center, encapsulated by connective tissue infiltrated with lymphocytes In one portion there is a nodule of cells resembling adrenal cortex Sections of the glandular portion of this gland show several areas of tuberculosis with caseation and epithelioid and giant cells There are a few cells in places which resemble adrenal cortex but most of the cells resemble adrenal medulla

Bacteriology—Cultures from the heart's blood remain sterile

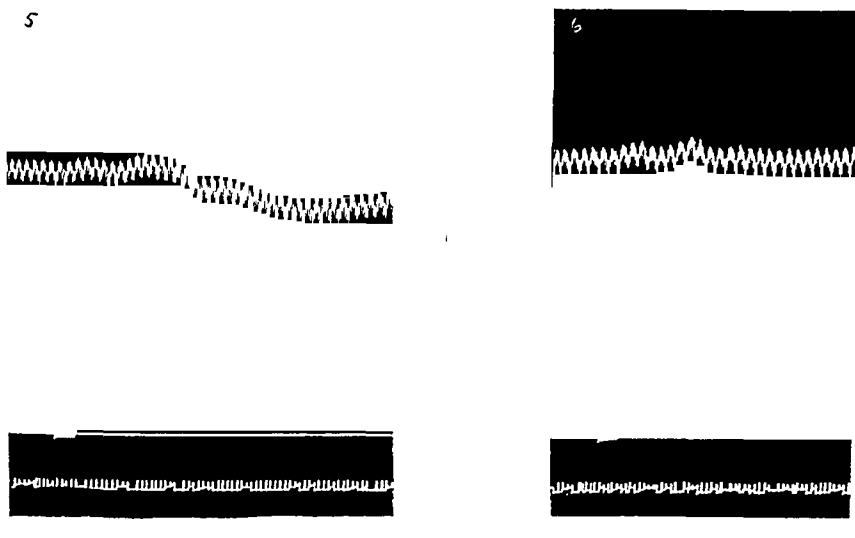

Fig 5—Injection of second extraction of normal appearing portion of right adrenal

Fig 6—Injection of second extraction of tuberculous portion of right adrenal Dog 2

ANATOMICAL AND MICROSCOPICAL DIAGNOSIS

Tuberculosis of adrenals and liver Edema of brain Bronchopneumonia Scar at apex of right lung Chronic adhesive pleuritis Chronic obliterative appendicitis

It was thought of interest to determine if possible, whether the adrenals from this case contained the usual blood-pressure raising substance, and if so, whether the amount was the same as that from normal human adrenals Accordingly, the adrenal tissue present was divided into three portions The first consisted of 1 5 gm of the normal-appearing portion of the right adrenal, the second of 8 gm of the tuberculous portion of the same gland, and the third consisted of about 0 5 gm of the left adrenal Each of these was ground up in a mortar with sea-sand, glass and ten volumes of normal salt solution Each was then centrifugalized in a high-power centrifuge and the supernatant fluid used for the experiments A second extraction of the residue was made in a similar manner and kept separately These extractions were done immediately and kept on ice The following day a small dog was anesthetized and blood-pressure was taken from

the femoral artery Injections of 2 c c of each of the extracts were made into the femoral vein Tracings were also made from similarly prepared extracts of adrenals from three cases which showed no gross or microscopic adrenal lesion One of these individuals died from chronic valvular disease of the heart, one from acute encephalitis and one from acute lobar pneumonia For comparison, in each case one minim of a solution of epinephrin (adrenalin, 1 1000 Parke, Davis & Co) was injected, the same solution being used each time

The extract from the much atrophied left adrenal, which microscopically showed principally medullary cells, caused a slight but definite rise in blood pressure (Fig 3), while the extract of the tuberculous part of the right adrenal caused none (Fig 4)

The tracings from the normal appearing portion of the right adrenal (Fig 2) showed that it contained blood pressure raising substance, and that the rise in pressure obtained with 2 c c of the extract from this portion of the gland was quite similar to that caused by the injection of one minim of epinephrin solution (1 1000) (Fig 1) Each of the three tracings made from the normal adrenal extracts, however, gave a much more marked rise in pressure than that obtained from one minim of epinephrin solution (1-1000) (Figs 7 and 8) No rise in pressure followed injections of the second extraction of the tissue (Figs 5 and 6) It was assumed that all the principle had been obtained in the first extract

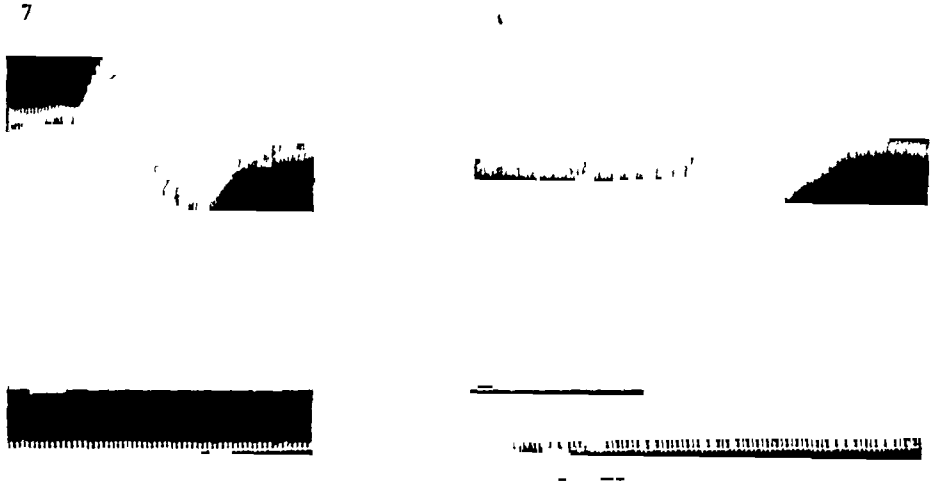

Fig 7 —Injection of 1 minim of epinephrin solution (1 1000)
Fig 8 —Injection of extract of normal adrenal gland

It seems probable that in this case, although a portion of adrenal tissue having a relatively normal appearance remained uninvolved in the tuberculous process, yet demands were made for adrenal secretion which this small amount of remaining tissue could not supply and that there ensued an acute adrenal insufficiency That there was a diminution in the blood pressure raising substance contained in the glands, as compared with normal glands, indicates that the deficiency may have also involved the other functions or other internal secretion of the adrenal, but of this one can only conjecture It is interesting that there were no histological evidences of any abnormality in the other organs of internal secretion

In some respects the above case is analogous to a case of experimental acute insufficiency of the parathyroid glands that I observed during the past year [3] In the experimental case, two operations were performed on a dog at an interval of about three weeks At the first operation, two

3 Cooke Jour Exper Med , 1911, xiii, 439

parathyroids were removed from each side As the animal developed no symptoms, a second operation was performed and one lobe of the thyroid was removed The animal recovered rapidly from the operations and showed no symptoms of parathyroid insufficiency, except a slight increase in reflexes and in muscle irritability Ten months afterward, however, the dog suddenly developed violent tetany with vomiting, dyspnea and convulsive attacks, and died after three days At autopsy no lesions were found Serial sections of the remaining thyroid lobe showed a small imbedded parathyroid about 1 mm in diameter

It was assumed that in this case, the small amount of parathyroid tissue remaining had been sufficient for the ordinary needs of the animal, and when, from some unknown cause, the demand for parathyroid secretion by the organism exceeded the capabilities of this small nodule, an acute fatal parathyroid insufficiency developed

In 1895 Oliver and Schafer[4] found that injections of the extracts of the fibrocaseous adrenals from a case of Addison's disease had no effect on blood-pressure, and Crowell[5] made a like observation in two similar cases I have been able to find no other physiological study of diseased adrenals

If one can compare the tracings obtained by injections of extracts of adrenal glands made post mortem, the marked difference observed in the extracts of normal adrenals and that of the tuberculous adrenals from the case here reported indicate that there was a rather marked functional deficiency in the latter and that this decreased function involved even adrenal tissue which showed no gross or microscopic lesion

I wish to thank Professor R M Pearce of the Department of Research Medicine in the University of Pennsylvania for the privileges of his laboratory, and Dr A B Eisenbrey of the same department for his assistance in making the tracings

4 Oliver and Schafer Jour Physiol , 1895, xviii, 230
5 Crowell Proc New York Path Soc , 1909, new series, ix, 75

THE DETERMINATION OF INDIVIDUAL DOSAGE IN TUBERCULIN THERAPY

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PITTSBURGH

A year ago we published a report of a year's study on a method to obtain a uniform reaction to tuberculin in patients of widely different character, both as regards extent of disease and physical condition.[1] The method outlined in this and previous papers was an effort to obtain a *specific, individual, biological test of the therapeutic doses of tuberculin*, which would give uniform results in patients requiring this form of treatment. The basis of this method was laid in the varying sensitiveness to tuberculin, which was found by numerous observers to exist in the surface cells of individuals *suffering from tuberculosis*. We felt that such a method, if it could be evolved, would at least get rid of the tedious method formerly in vogue of starting all patients on an exceedingly small dose and gradually working up over a period of many months to a dose which bordered on reaction or which produced a tolerance to the poison. It would thus save many months in treatment, provided one is willing to grant that the very small doses are of very little or no value in producing the results which were desired in the therapeusis of tuberculosis with tuberculin. We felt, however, that there was a wider field of value in this method, viz., the possibility of producing a measured grade of reaction which many had come to feel was the necessary thing in any vaccine treatment. Such a conclusion necessarily required more or less arbitrary determination of the grade of reaction which was valuable, of the interval which should elapse between dosage, and of the ultimate object to be obtained in tuberculin treatment.

We submitted in our last year's paper certain of these arbitrary conclusions which required further study and elucidation before they could be finally accepted. We shall report here the results of another year's work in continuation of the lines laid down in our former paper.

The results of this year's work have fully confirmed our belief that all that we offered in our last year's paper is correct, not only in principle but in the beneficial effect resulting from such treatment.

The principle in which we believe in tuberculin therapy, is that the object to be obtained is the reaction of the body cells which results from

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*From the King Edward VII Memorial Laboratory of the Tuberculosis League of Pittsburgh, with funds provided by Mr. R. B. Mellon.

1. White and Van Norman, THE ARCHIVES INT. MED., 1910, vi, 449.

a sufficient dose of tuberculin, and *not* the tolerance which comes from gradually increasing dosage

The method outlined in our former paper was first to determine the sensitiveness of the individual to tuberculin by using on the skin a definite quantity of varying dilutions of tuberculin, then, having arrived at the dilution which, with a given technic, would give a minimal cutaneous reaction around the point of scarification, to determine on this basis the quantity of tuberculin which could be given subcutaneously to produce a reaction of required degree

The requisites in the technic of this determination were

1 A throttle pipette which would measure exactly 0 01 c c of the given dilution of tuberculin

2 The tuberculin to be a solution of the tuberculin poison and not a suspension (During the past two and a half years we have used Old Tuberculin)

3 All dilutions of tuberculin to be carefully and freshly made on the basis of pure Old Tuberculin containing 1,000 mg of the substance desired to the cubic centimeter

4 The scarification to be made before the application of the tuberculin and of a depth sufficient to penetrate to the corium, producing a pink spot of definite measurement without drawing blood or serum

5 Contemporaneous scarifications not to be in the same line of lymphatic drainage

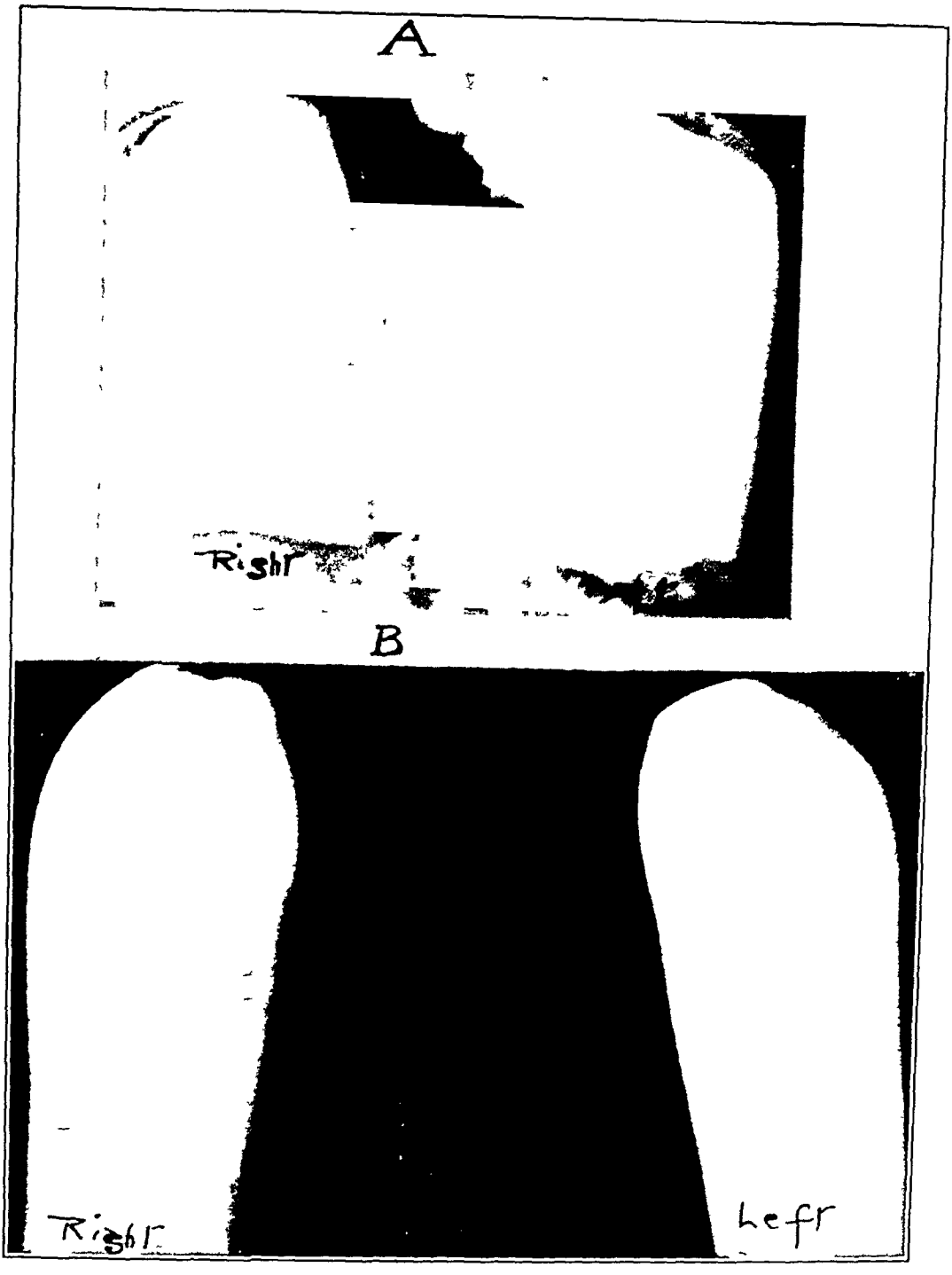
6 Therapeutic doses determined on the basis of minimal cutaneous reaction to be given from the same strain of tuberculin as that on which the minimal cutaneous reaction was determined

7 The protection, by some such method as a vaccine shield to allow for uniform absorption,[2] of the point of scarification on which the tuberculin is placed

TECHNIC IN OBTAINING MINIMAL CUTANEOUS REACTION BASED ON SENSITIVENESS OF THE INDIVIDUAL TO TUBERCULIN

The inner side of either forearm is used, and if more than one test is necessary to determine the minimal cutaneous reaction it is best to use the arms alternately Before scarifying the skin is washed over with alcohol The scarification is made by a von Pirquet scarifier and is done with just enough force to pierce the upper layer of the skin leaving a punctate spot measuring 2 mm in diameter, the base of which shows bright pink in color No blood should be drawn The obtaining of this pinkness at the base of the scarification is of importance Scarification any deeper is not necessary but if it is any less there is not the proper

2 White and Graham Jour Med Research 1909 xx 347



Figures 1 and 2

To show the ratio between the size of reaction and amount of tuberculin used in modified von Pirquet tests A, Case 1, B, Case 2 In both cases 3 per cent O T was used On the left arm 0 01 c c was applied and on the right arm 0 03 c c It will be noted that the resulting reactions vary about three times In Case 1 the reaction on the left arm in 72 hours averaged 12 mm and on the right arm averaged 35 mm In Case 2 the reaction on the left arm in 72 hours was 8 mm and on the right arm was 23 mm, i e, in both cases the reaction on the right arm was three times as great as that on the left arm, and in both cases there was three times as much tuberculin used on the right arm as on the left The other dark spots are the result of adhesive plaster

removal of the dead cells to allow absorption of the tuberculin It is advisable to wait, before making the application of tuberculin, for half a minute after making the scarification, to be sure that the correct depth has been obtained

The next step is to apply with a throttle pipette a drop measuring exactly 0 01 c c of the tuberculin solution to be used This is applied exactly over the point of scarification and is then covered with a vaccine shield kept in place by two strips of adhesive, and the patient directed to hold the arm in a horizontal position until the drop has dried Readings are taken at the end of twenty-four, forty-eight and seventy-two hours, and the amount of reaction accurately measured in millimeters A control scarification is always made below the scarification for the application of tuberculin All patients should be tested first with a 1 per cent solution

If there is no reaction at the end of seventy-two hours to 1 per cent, one may use a 2 per cent solution, or higher if necessary If at the end of seventy-two hours the 0 01 c c of the 1 per cent solution produces exactly a minimal cutaneous reaction, it is of course unnecessary to do any further testing, but if 1 per cent causes larger than a minimal cutaneous reaction, the next test can be made with 0 5 or 0 25 of 1 per cent, using diminishing solutions until the minimal cutaneous reaction is obtained

If time is a factor in obtaining the beginning dose for treatment, two solutions may be applied at the same time on the same arm, and in such case it is well to use 1 per cent and 0 25 per cent If two solutions are used, it must be remembered to place the weaker solution below (distally) Table 1 shows the result of applying 1 per cent and 0 25 per cent O T on the same arm at the same time

TABLE 1—SHOWING METHODS USED IN CHARTING RESULTS FOR RECORDS *

1 SKIN TESTING TO DETERMINE MINIMAL CUTANEOUS REACTION

Date	Skin Test † Modified von Pirquet	Result	Appearance of Reaction	
			Size (mm)	Color
1/1/11	L U 1 per cent O T			
	L L 0 25 per cent O T			
1/2/11	L U reaction in 24 hours	Positive	5x4	Slight redness
	L L reaction in 24 hours	None		
1/3/11	L U reaction in 48 hours	Positive	6x5	Moderate redness
	L L reaction in 48 hours	Slight	2	Slight redness
1/4/11	L U reaction in 72 hours	Positive	7x7	Moderate redness
	L L reaction in 72 hours	Slight	2 5	Slight redness

2 TUBERCULIN ADMINISTRATION THERAPEUTICALLY

Jan 15, 1911, tuberculin, 00005 gm , O T Jan 16, 1911 local redness 2 5x2 cm , moderate , local tenderness, slight , local swelling, moderate Jan 17, 1911, local redness 4x3 cm moderate , local tenderness moderate , local swelling moderate constitutional symptoms, none , sputum in 24 hours less 10 per cent , in 48 hours, less 33⅓ per cent

* 1 per cent O T causes 7 mm reaction in 72 hours and 0 25 per cent O T causes 2 5 mm reaction Therefore the minimal cutaneous reaction is = 0 5 per cent

† L U = left arm, upper test , L L = left arm, lower test

As the 1 per cent solution caused more than 4 mm reaction and the 0.25 of 1 per cent showed very little reaction, therefore the minimal cutaneous reaction was determined as 0.5 per cent

If the tests are given singly, and it is necessary to give more than one test to determine the minimal cutaneous reaction, a week should always be allowed to elapse between the tests

We call a minimal cutaneous reaction one which gives redness, with some induration, measuring exactly 4 mm in diameter within seventy-two hours We have found very few cases in which it is necessary to give only one test to determine the minimal cutaneous reaction, and during the past year all cases of tuberculosis which came under our observation have given minimal cutaneous reaction to 5 per cent or less

RELATION OF DOSAGE OF TUBERCULIN AND MINIMAL CUTANEOUS REACTION

The quantity of tuberculin contained in 0.01 c c of that definite solution of tuberculin which will produce exactly the minimal cutaneous reaction which we call 4 mm in redness and induration at the site of application of the test will produce, when given subcutaneously, an area of redness, tenderness and swelling measuring from 2 to 5 cm in diameter Table 2 shows this relation

TABLE 2.—SHOWING RELATION BETWEEN MINIMAL CUTANEOUS REACTION AND THERAPEUTIC DOSE OF TUBERCULIN

Percentage of Tuberculin (O T) Producing Minimal Cutaneous Reaction	Actual Amount of O T Applied to Skin	Therapeutic Dose of O T
0.05	1/200 milligram	1/200 milligram
0.075	3/400 milligram	3/400 milligram
0.1	1/100 milligram	1/100 milligram
0.25	1/40 milligram	1/40 milligram
0.5	1/20 milligram	1/20 milligram
0.75	3/40 milligram	3/40 milligram
1	1/10 milligram	1/10 milligram
2	2/10 milligram	2/10 milligram
3	3/10 milligram	3/10 milligram
4	4/10 milligram	4/10 milligram
5	1/2 milligram	1/2 milligram

That is, a patient showing minimal cutaneous reaction to 0.01 c c of a 1 per cent solution of O T has 0.10 mg O T applied on the skin The corresponding therapeutic dose for this patient is 0.10 mg O T and if 0.10 mg O T is given subcutaneously, there will be a resulting local reaction of from 2 to 5 cm within forty-eight hours

By this method it is possible to determine a dose of tuberculin for each case which will produce exactly the same degree of local reaction in all individuals It will allow the determination of a perfectly safe dose varying at least 100 times in quantity During the past year we have confirmed the studies mentioned in last year's paper that in tuberculin

dosage there is, in individuals, a variation of the primary dose from at least 0.005 to 0 5 mg of tuberculin to produce the same amount of local reaction

We have been disappointed that the method which we have outlined and used with so much satisfaction ourselves, has not been such as to meet with success in the hands of the general practitioner, and we have this year had many communications asking for explanations of difficulties which have been encountered in utilizing this method

It has been clearly demonstrated to us during the past year that it is necessary for those who wish to use this quantitative method to be thoroughly familiar with tuberculin work and the necessity for the utmost care in making dilutions

One of the greatest difficulties we have experienced in advocating this method is to get other investigators to appreciate the fact that the definite quantity of tuberculin which we use in obtaining the minimal cutaneous reaction, i e, 0 01 c c measured by a throttle pipette, is important not because a little more or less in quantity would vary the cutaneous reaction to a marked degree, but that it gives us a measured quantity of tuberculin on which to base our therapeutic dose

Von Pirquet has repeatedly and lately in his article in Krause and Levaditi,[3] called attention to the fact that he does not consider this measured quantity important, but he has failed to appreciate the fact that without this measured quantity there could be no ratio for a definite therapeutic dose On the other hand von Pirquet and others have stated that the quantity of tuberculin used in obtaining the cutaneous reaction is not an important factor, but we have found repeatedly, as the accompanying illustrations demonstrate, that this is an exceedingly important factor in the size of the reaction obtained, provided the other features of technic have been observed

It seems likely to us that the chief difficulties which others have encountered in obtaining like results from the therapeutic doses which we have described in our former paper have arisen chiefly from errors in technic

1 Failure to measure accurately the 0 01 c c of tuberculin in obtaining the minimal cutaneous reaction Without this the method which we have advocated is, of course, useless, because the therapeutic dose is the quantity of tuberculin which is contained in 0 01 c c of a given dilution which will exactly produce a minimal cutaneous reaction (see Table 2) No approximate drop will allow the determination of the ratio of the therapeutic dosage which is later to be given

2 Failure to obtain a uniform depth of scarification in the skin tests

3 Krause and Levaditi Handbuch der Technik u Methodik der Immunitätsforschung p 197 Jena 1908

3 Failure to obtain exactly the minimal cutaneous reaction, i e. exactly 4 mm in diameter.

4 Failure to read the skin test up to the end of seventy-two hours

5 Inaccuracy in making the dilutions of definite strength, both for the skin test and for the therapeutic dose We would call attention to the fact that two sets of solutions are used one for skin-testing and the other for the therapeutic doses of tuberculin The former are straight percentage solutions 5, 4 3, 2, 1 to 0 05 per cent The latter are made in sequence, so that 1 c c of each solution equals 1 mg or more, or a fraction of a milligram For example 1 c c of Bottle 1 equals 100 mg 1 c c of Bottle 2 equals 10 mg, 1 c c of Bottle 3 equals 1 mg, 1 c c of Bottle 4 equals 0 1 mg, etc

6 In administering tuberculin, forgetting that the therapeutic dose must be an intracutaneous one to give the grade of response which we have described, and not a deep subcutaneous or intramuscular dose

7 Failure to allow at least a week to elapse between the final reading of the skin test and the first therapeutic dose of tuberculin

In addition to these points, it is necessary, of course, to allow fourteen days to elapse between therapeutic doses

From certain unknown causes patients vary in sensitiveness, even under treatment, from time to time, consequently the therapeutic reactions are not always of exactly the same size, variations of 1 to 2 cm in the therapeutic reactions following each other at stated periods being quite common, and yet a more pronounced reaction may be followed by a less pronounced reaction and this followed for many months again by a reaction of the same grade which is desired for the patient We feel that all patients under tuberculin treatment should have their dose confirmed or changed by means of determination by the skin test every three months

It will be noted that all but two of these patients gained in weight — these two instances being Patient 8 and Patient 30 Patient 8 was much above normal weight at 130 pounds In Case 30, tuberculin treatment until January At that time she had many severe hemorrhages and lost 26 pounds in weight Tuberculin was discontinued and has not been given since

Case 33 shows the greatest number of therapeutic doses given extending over the longest period of time This case is of interest inasmuch as the same dose of tuberculin which is marked in the table was given for six months prior to Jan 29, 1910, each time with a local reaction of between 3 and 4 cm This dose was really arrived at arbitrarily in July, 1909, and in January, 1910, as the table shows, the skin test was given to determine the minimal cutaneous reaction which was found to be 1 per cent The same dose, 0 1 mg O T, was continued This means that Case 33 has had thirty-five injections of the same dose of tuberculin

TABLE 3.—SHOWING (1) VARIATION IN EXTENT OF DISEASE, AGE AND SENSITIVENESS (PER CENT OF TUBERCULIN GIVING MINIMAL CUTANEOUS REACTION) (2) DOSAGE BASED ON SENSITIVENESS (3) LENGTH OF TIME OF TREATMENT WITH CONSTANT SIZED REACTION BASED ON SENSITIVENESS

Case Number	Classification N A	Classification Turban	Age	Sex	Number of Hospital Days	Date of First Skin Test	Date Minimal Cutaneous Reaction Was Obtained	Number of Skin Tests to Determine Min Cutaneous Reaction	Per Cent of Tuberculin Giving Minimal Cutaneous Reaction	Date of First Therapeutic Dose of Tuberculin	Therapeutic Dose of Tuberculin (O T) in Gm	Average Size of Reaction on First Dose in Centimeters in Forty-Eight Hours	Length of Time of Constant Reaction to Same Dose (mos)	Change in Sensitiveness to Tuberculin More	Change in Sensitiveness to Tuberculin Less	Number of Treatment Doses to Date	Dose Changed From	Dose Changed To	Weight Adm	Weight Dis	Weight Gain	Weight Loss
1	Adv	2	24	F	723	3/ 6/09	4/ 5/10	3	0 25	4/13/10	000025	2	4			6			115	120¾	5¾	
2	Adv	2	20	F	470	3/23/09	3/29/10	2	0 5	4/13/10	00005	3 5	4			6			115½	123¼	7¾	
3	Far adv	3	21	M	227	7/29/10	10/ 8/10	2	0 5	10/13/10	00005	2 5	4			7			121½	133	11½	
4	Adv	2	22	F	485	10/ 8/09	4/ 3/10	2	0 1	4/13/10	00001	2 5	4		+	8	00001	000025	97	118	21	
5	Adv	2	51	F	174	10/24/10	10/24/10	2	0 25	11/ 1/10	000025	2 5	4			8			95	106¼	11¼	
6	Adv	2	25	M	187	9/ 7/10	12/ 5/10	2	0 25	12/14/10	000025	3 5	4			6			131	163½	32½	
7	Far adv	3	17	F	759	3/24/09	9/18/10	2	1	9/29/10	0001	2	4			8			83	87	4	
8	Adv	2	31	F	165	11/21/10	11/21/10	2	1	11/29/10	0001	2 5	4			7			130	127		3
9	Incip	1	20	M	162	11/21/10	12/ 5/10	4	0 5	12/14/10	00005	3	4			6			141	158½	17½	
10	Adv	2	13	F	959	6/ 3/09	4/ 3/10	4	0 25	4/13/10	000025	4	5			7			70¾	106	35¼	
11	Adv	2	23	M	166	9/18/10	9/18/10	2	0 5	9/24/10	00005	2 5	5			10			115¼	133¼	18	
12	Adv	2	23	F	159	11/21/10	11/21/10	2	1	11/29/10	0001	2	5			6			134½	137	2½	
13	Far adv	3	26	F	252	2/13/10	1/ 5/10	6	0 1	4/27/10	00001	2 5	6			8			112¼	117¾	5½	
14	Adv	2	22	M	1,227	2/26/09	2/15/10	2	5	2/24/10	0005	3	6			11			105	125¾	20¾	
15	Far adv	3	35	F	713	4/19/09	3/31/10	3	1	4/13/10	0001	3	6			9			105	121¾	16¾	
16	Incip	1	17	F	133	2/13/10	7/29/10	2	0 25	8/18/10	000025	2 5	6			13			111¼	113½	2¼	
17	Far adv	3	20	F	367	3/25/10	8/26/10	3	0 5	9/ 1/10	00005	2	6			10			110¼	146	35¼	
18	Adv	2	17	M	256	5/17/10	8/ 4/10	2	0 25	8/18/10	000025	3	6			10			70¾	110	39¼	
19	Adv	2	9	F	541	7/24/09	1/ 5/10	4	0 1	4/13/10	00001	2	6		+	9	00001	000025	52	78½	26½	
20	Adv	2	19	M	216	10/ 8/10	10/ 8/10	2	1	10/13/10	0001	2	6			10			128	148	20	
21	Adv	2	21	M	371	3/10/10	8/ 4/10	2	0 25	8/18/10	000025	2 5	6			13			118	138	20	
22	Far adv	3	28	F	287	8/ 4/09	3/31/10	1	0 25	4/13/10	000025	3	7		+	13	000025	00005	109	145½	36½	
23	Adv	2	17	F	360	5/17/10	7/29/10	2	0 25	8/18/10	000025	2 5	7			13			101¼	112	10¼	
24	Adv	2	20	M	1,155	3/26/09	8/11/10	3	2	8/18/10	0002	3	8			16			123	151	28	
25	Adv	2	24	M	276	8/22/10	8/25/10	2	2	9/ 1/10	0002	3 5	8			12			97	104	7	
26	Far adv	3	21	M	285	5/17/10	5/17/10	1	1	5/25/10	0001	2	8			11			157	170¼	13¼	
27	Incip	1	24	M	280	8/ 3/10	8/ 3/10	2	0 5	8/ 6/10	00005	5	9			18			136	138½	2½	
28	Adv	2	51	F	106	3/16/09	1/ 3/10	2	0 5	4/13/10	00005	2	9			17			100¼	*	*	
29	Incip	1	24	M	365	12/13/09	2/ 6/10	4	0 1	3/29/10	00001	3	11			18			158	172	14	
30	Far adv	3	16	F	646	8/ 4/09	1/14/10	2	0 5	1/27/10	00005	2 5	11			10			126	100		26
31	Far adv	3	22	M	971	3/23/09	3/ 3/10	4	0 5	4/13/10	00005	3	12			19			127	135	8	
32	Incip	1	32	M	100	5/19/09	3/13/10	3	0 1	4/ 9/10	00001	3	13			27			130	150	20	
33	Adv	2	35	M	900	1/26/09	1/20/10	2	1	1/29/10	0001	5	15			27			152	164	12	

* Not weighed

(0 1 mg) extending over a period of twenty-one months with constant degree of reaction

It should be noted that these cases fall under three classes incipient, advanced and far advanced, and that the age varies from 9 to 54 years, that the length of constant reaction to the same dose varies from four to fifteen months, and that the average size of the reaction on the first therapeutic dose shows very little variation — from 2 to 5 cm

In Cases 4, 19 and 22 it will be noted that there have been variations in the sensitiveness of the patients All three of these patients have become less sensitive The variation was first noticed with the therapeutic dose and was later verified by the minimal cutaneous reaction to be actually a change in the sensitiveness of the surface cells This subject will be taken up later in the discussion of Table 4

TABLE 4 —SHOWING (1) THE WIDE VARIATION IN SENSITIVENESS TO TUBERCULIN BASED ON MINIMAL CUTANEOUS REACTION, AND (2) VARIATION IN DOSAGE WHICH WILL GIVE APPROXIMATELY THE SAME REACTION IN PATIENTS DIFFERING IN EXTENT OF DISEASE *

Case Number	Age	Sex	Classification		Per Cent of Tuberculin Giving Minimal Cutaneous Reaction	Therapeutic Dose of Tuberculin (O T) in Gm	Result					
							In 24 Hours			In 48 Hours		
			National Association	Turban			Local Redness, Size in Cm	Local Tenderness	Local Swelling	Local Redness, Size in Cm	Local Tenderness	Local Swelling
1	37	F	Far advanced	3	0 05	000005	2x1 5	M	M	2 5x1 5	M	M
2	8	F	Incipient	1	0 075	0000075	3x2	Sl	M	3 5x2 5	M	+
3	11	F	Incipient	1	0 075	0000075	2 5x1 5	Sl	M	2 5x2	Sl	M
4	45	F	Far advanced	3	0 075	0000075	1 5x1	M	M	2 5	M	M
5	40	F	Advanced	2	0 075	0000075	3x2	Sl	M	3	M	M
6	10	F	Incipient	1	0 1	00001	3x2	M	+	4 5x3 5	M	+
7	30	M	Incipient	1	0 1	00001	2 5x2	M	M	3 5x3	M	M
8	10	M	Incipient	1	0 15	000015	2x1 5	Sl	M	2 5x2	Sl	M
9	12	F	Incipient	1	0 2	00002	2x1 5	M	M	2	M	M
10	50	F	Advanced	2	0 2	00002	2 5x1 5	M	+	2 5x2	M	+
11	18	F	Advanced	2	0 25	000025	2 5	M	M	4	M	M
12	25	M	Advanced	2	0 25	000025	2 5	M	Sl	3 5	M	M
13	26	F	Advanced	2	0 3	00003	2 5x2	Sl	M	5	+	+
14	25	M	Far advanced	3	0 5	00005	3x1 5	Sl	M	3x1 5	M	M
15	25	F	Advanced	2	0 5	00005	3x1 5	M	M	3 5x2 5	M	M
16	10	F	Incipient	1	0 75	000075	3 5x2 5	M	M	5	M	+
17	23	F	Advanced	2	1	0001	2x1	M	M	2 5x1 5	M	M
18	31	F	Advanced	2	1	0001	3x2 5	M	M	3	M	M
19	30	M	Advanced	2	1	0001	2 3x2	Sl	M	3x2	M	M
20	23	M	Advanced	2	2	0002	2 5x2	Sl	Sl	3	M	Sl
21	25	M	Advanced	2	2	0002	3x2 5	M	Sl	5x3 5	M	Sl
22	25	M	Far advanced	3	3	0003	2	M	Sl	3 5x3	M	Sl
23	15	F	Incipient	1	4	0004	4	M	M	4	+	+
24	25	M	Advanced	2	5	0005	1 5x1	M	Sl	4	+	+

(Note difference in age of patients)
* In this table Sl means slight, M, moderate, and + marked

We have included in Table 3 only thirty-three patients out of a total of 161 individuals who have been treated during the past year on this basis If all the 161 cases were tabulated it would simply be a dupli-

cation of the thirty-three as shown here which have been chosen at random from the whole series

Table 3 shows clearly that, having obtained in each patient a minimal cutaneous reaction (4 mm in measurement in each case) to 0 01 c c of a definite solution of tuberculin, the same quantity of tuberculin introduced subcutaneously gives in all patients a local reaction of from 2 to 5 cm at the point of inoculation

The results in this table show the variation in degree of sensitiveness in twenty-four cases It will be noticed that the patients vary in age from 8 to 50 years, in amount of disease from incipient to far advanced, in degree of sensitiveness (as shown by the minimal cutaneous reaction to 0 01 c c) from 0 05 of 1 per cent to 5 per cent, a difference of 100 times, and in dosage, based on the quantity of tuberculin contained in 0 01 c c, from 0 005 mg of tuberculin to 0 5 mg of tuberculin, a difference in quantity of 100 times, resulting in approximately the same degree of local reaction at the point of inoculation of the therapeutic dose

The results in these twenty-four cases, which have been chosen to show the wide variation in sensitiveness, were duplicated in each of the 161 individual patients who have been under this treatment during the past year There is no possibility of grading the dosage of tuberculin according to the extent of disease In other words, the variation of sensitiveness is a more subtle thing than the variation in extent of involvement

The past year s work has determined the following points

1 It will be seen that these tables verify our contention in former papers that it is possible to determine the quantity of tuberculin on the basis of the minimal cutaneous reaction which will give the same result in any group of patients requiring tuberculin treatment, even though these patients differ in their sensitiveness in wide degree

2 The reaction response having been determined to an individual dose of tuberculin in any given patient, this patient continues to react in the same way to the same dose given every fourteen days for periods as high as twenty-one months, which is the longest time any individual has had tuberculin under this method and the vast majority of patients continue to react in the same way to the same dose given every fourteen days without change in the character of the reaction

3 In a few cases which have been under observation during active disease and arrested disease (National Association Classification) we have found that these cases lose their sensitiveness to tuberculin after becoming arrested, and that increasing doses may be given every fortnight with the same or diminishing local reaction as obtained formerly by the therapeutic dose determined on the minimal cutaneous reaction basis It occurred to us that it would be of interest to increase the dose in such patients and subsequently test the skin sensitiveness of these patients to

determine whether the relation of skin sensitiveness to the therapeutic dose was present We were able to make this investigation in only two cases

CASE 1.—Patient, male, aged 30, with a lesion, advanced, Turban II The original dose of tuberculin determined on skin sensitiveness was 0 05 mg O T After the case became arrested (National Association Classification) the sensitiveness became less until finally the patient was given 4 mg—this after a period of a year in which no determination had been made of his skin sensitiveness To 4 mg he had a local reaction of 3 cm with absolutely no constitutional reaction of any kind Two weeks after he was given the 4 mg he was given 0 01 c c of 40 per cent O T on the skin, and gave a reaction of 5×4 mm within seventy two hours

CASE 2.—Patient, male, aged 24, with a lesion, advanced, Turban II This patient had been under tuberculin treatment for two years When first coming under observation the case was quite active, but for the past six months has been an arrested case (National Association Classification) The original dose of tuberculin given was 0 025 mg O T As the patient's sensitiveness diminished, the dose was increased until he was getting 1 mg O T On 1 mg the local reaction measured 3 5 cm at the point of inoculation Two weeks after this was administered, he was given 0 01 of 10 per cent O T on the skin, the resulting reaction being 4 mm

Patient 1 was a private patient living some distance from Pittsburgh, and it was impossible to keep him under longer observation In Case 2 a therapeutic dose of 1 mg was given fourteen days after the skin test of 10 per cent was administered, and the patient again showed a local reaction at the point of inoculation of 3 5 by 2 5 cm

4 We were unable before this year's work to state with any degree of certainty the partition dose of tuberculin on the basis of the minimal cutaneous reaction which would give no reaction at the site of injection In our last paper we suggested that, on the basis of a few cases, one-tenth of the minimal cutaneous dose would produce no local reaction The partition dose we have found during this year's work to be one-thirtieth of the amount of tuberculin used to obtain the minimal cutaneous reaction, as will be seen by Table 5

From Table 5 it is seen that the dose of tuberculin must be reduced to one-thirtieth of the dose causing 2 to 5 cm of reaction before all patients refuse to react

5 In our last paper we stated that ten times the minimal cutaneous reaction dose of tuberculin given subcutaneously would cause constitutional as well as local reaction Necessarily this figure is more difficult to determine in the patients than the fraction of the minimal cutaneous dose which would cause no reaction, but in a few cases during the past year we have seen that this figure of ten times is correct In fact, in one case four times the minimal reaction dose, given subcutaneously, caused slight constitutional reaction We bring this point out especially to show how near the border-line of general reaction it is possible to go with a therapeutic dose given on the basis of a minimal cutaneous reaction

TABLE 5—SHOWING THE PARTITION DOSE OF TUBERCULIN ON THE BASIS OF MINIMAL CUTANEOUS REACTION WHICH WILL GIVE NO REACTION IN PATIENTS *

Date	Number of Patients Given Tuberculin	Fraction of Minimal Cutaneous Reaction Dose	Reaction	Per Cent	No Reaction	Per Cent	Remarks
2/22/11	44	1/10	33	75	11	25	Redness—Size varied from 0 5 to 3 cm , average, 1 2 cm , slight in degree
3/8/11	44	1/20	24	55	20	45	Redness—Size varied from 1 to 3 cm , average, 1 cm , very slight in degree
4/5/11	28	1/50			28	100	
4/19/11	8	1/40			8	100	
4/19/11	24	1/30			24	100	

* It will be seen that 1/10 of the quantity of tuberculin producing the minimal cutaneous reaction causes local reaction in 33, or 75 per cent of the cases, 1/20 causes local reaction in 24, or 55 per cent of the cases, and 1/30 gives no reaction whatever

6 In a series of forty-six cases the therapeutic injection of tuberculin was given deeply in the triceps muscle There was in these cases, as would be expected, no visible redness and swelling, and in only a few cases was there even the slightest tenderness at the site of inoculation It might have been expected that the more rapid absorption of tuberculin from the intramuscular injection would produce a constitutional reaction, but this was not so in any case

This point has strengthened our belief in the supposition that there is something in the response which the skin cells make to the injection of tuberculin which is valuable in this form of medication

We have for some years had the impression, without being able to devise experiments to prove it, that the antibodies which accompany therapeutic usage of tuberculin are mainly produced by the skin cells, and that produced around the site of the injection of tuberculin, is the reaction which produces the substances which result in the beneficial effect of the response, as evidenced by redness tenderness and swelling which is tuberculin dose

It will be interesting to follow the lead of Auer and Meltzer[4] in testing the absorption from intramuscular tissue in various regions with the possibility that it may be found that reaction and absorption may vary in muscles in different parts of the body

We have not yet been able to demonstrate that provided the patient remains quiet, there is any variation in the sensitiveness of the surface cells in different parts of the body either to skin test or to therapeutic

4 Auer and Meltzer Jour Exper Med 1911 xiii 328

doses given intracutaneously Having once determined the quantity of tuberculin which will produce a certain grade of reaction, it will produce this grade of reaction in any part of the body which we have yet tried Naturally this applies only to those parts of the body, such as legs, arms or trunk, where such injections would be likely to be given and not to such parts of the body as hands and feet, where the peculiarity of the skin surface is marked

ATYPICAL CASES

In the past year there have been three cases in which the therapeutic dose on the basis of the minimal cutaneous reaction has been larger than we expected We have no explanation to offer for the failure of these cases The sensitiveness was determined in the usual way i e by means of the skin test, but the first therapeutic dose of tuberculin produced a much larger local reaction than we expected (over 5 cm) On returning to the skin test we found in each case that the skin sensitiveness was much greater than was obtained in the first test, i e, that the minimal cutaneous reaction was obtained to a much weaker solution of tuberculin than in the first test, and the second therapeutic dose of tuberculin determined by the second skin test caused the usual local reaction of from 2 to 5 cm

We are loath to suggest that this atypical condition arises from the technic of determination of dose as this has all been done by one of us and great care has been exercised in order to prevent such occurrence We have some suspicion that rapid changes in sensitiveness may occur in the body from causes other than the administration of tuberculin We shall hope to make a further report on these atypical cases at a later date

In this connection we desire to emphasize the necessity for the same person to determine all doses in any given group of cases, as the personal factor in this, as in all laboratory methods, is of importance For this reason we feel that judgment should be passed on the principles contained in this paper and not on the results of any one man failing to carry out the technic and precautions of this administration

EVIDENCES OF BENEFIT

In our patients, so striking has been the comparison of improvement between the present and the past that, when we compare the results from the administration of tuberculin based on the principle of securing reactions, and the results obtained in patients when we gave tuberculin with the desire of producing tolerance, we no longer have any doubt as to the proper method of administration It is the more or less constant result of the administration of tuberculin in the dose which will produce a mild reaction, that the patient feels better, coughs less, and expectorates less —

even so marked reduction in amount of sputum as 50 to 70 per cent in the forty-eight hours following tuberculin, being of frequent occurrence

Perhaps the most striking of all results of tuberculin administration is the improved resistance and ability of the patient to stand exercise and strain We feel that it is not too much to claim for this method of administration that it is the only plan of administration of tuberculin based on sound principles, and that it should rapidly supersede any attempt at auto-inoculation by exercise, which has in our hands, and in the hands of others, produced such dire results

It seems necessary to add a caution which we often take for granted as general knowledge, that tuberculin should only be given in suitable cases We feel that tuberculin should be given only to patients (1) whose maximum daily temperature does not exceed 99 6 F , (2) who are fairly well nourished, (3) whose general outlook seems favorable

CONCLUSIONS

1 It is possible by testing the sensitiveness to tuberculin of the surface cells of a tuberculous patient to determine the quantity of tuberculin which, when given subcutaneously, will produce a certain grade of reaction

2 It is possible to obtain the same grade of reaction in any given number of patients, even though the quantity of tuberculin to produce this reaction varies and the condition of the patient varies

3 The variation in the quantity of tuberculin necessary to produce the same grade of reaction in all cases is 100 times

4 It is not possible to determine by the extent of disease, age or condition of the patient the principle underlying this variation

5 The administration of tuberculin in doses which produce these mild (local) reactions has given the best results of any method of tuberculin therapy which we have used

BOOK REVIEW

MODERN TREATMENT The Management of Disease with Medicinal and Non Medicinal Remedies In Contributions by American and Foreign Authorities Edited by Hobart Amory Hare, M D Professor of Therapeutics and Materia Medica, Jefferson Medical College, Philadelphia, Assisted by H R M Landis, M D, Director of the Clinical Department of the Phipps Institute (University of Pennsylvania) In Two Volumes Vols I and II Cloth Price, $6 net Pp 1830, with 193 illustrations Philadelphia Lea & Febiger (1910)

So much labor and pains by wise and skilful men for no better result! What a pity! The day of compound books by many authors is past Any article good enough to be worth inclusion in such a work should be printed separately Landis' fine summary of the treatment of tuberculosis ought to be in the hands of thousands who can never buy these bulky volumes So with Riesman on typhoid and Leonard Rogers on plague They will not reach the readers who need them most

Most of the chapters are excellently done, particularly those written by clinicians who are not the partisans of any single therapeutic method Especially valuable are those by Meara on pneumonia and pleurisy, Dunn on meningitis, Potter on vaccine therapy, Joslin on diabetes and Sailer on stomach diseases

The articles on mineral springs, electrotherapy, rest cure and influenza are poor An uncritical, credulous and prejudiced spirit pervades them Especially out of place are the "General Considerations" on pharmacology toxicology and prescription writing, which seem to have strayed out of the last century Take for example this statement (Vol I, p 121) "When a patient is taking digitalis in full doses, he should be kept horizontal, as syncope is apt to occur on his suddenly assuming the erect posture" Anyone who has ever treated uncompensated heart disease knows that the erect or forward bending posture is the only one that can be assumed by a considerable proportion of those who need digitalis in full doses

In the section on hygienic measures, the statements about carbon dioxid (p 438) are quite out of date The otherwise excellent section on serum therapy contains no adequate reference to the phenomena of anaphylaxis, or to Crile's valuable suggestion of direct transfusion in obstinate oozing hemorrhage

The reviewer agrees with most of the views of Dr Potter, as to vaccine therapy but considers him overenthusiastic as to the value of antipneumococcus and antistreptococcus sera

With a considerable portion of Volume II, the present reviewer is not competent to deal (diseases of the eye, ear, and skin and tropical diseases, etc) Craig on the treatment of malaria is excellent, once he gets through with his section on diagnosis (it is an old failing of writers on treatment to succumb to the temptation to stray into fields of diagnosis)

The article on the treatment of syphilis is the best known to the reviewer That on the dysenteries is excellent

Mackensie on heart disease is suggestive and interesting but quite inadequate for the purposes of this book

Among misprints may be mentioned "adrenalin vein" for "adrenal vein" (Vol I p 569)

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STUDIES OF MALARIA IN PANAMA III THE ETIOLOGY OF THE ERYTHROLYTIC HEMOGLOBINURIC TYPE OF BLACKWATER FEVER*

A PRELIMINARY REPORT

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LOS ANGELES

Last year, in a paper[1] read before this society, I proposed that the terms "blackwater fever," etc, be abandoned, and that the fever more or less closely connected with malaria and accompanied by hemoglobinuria should be divided into two groups, "pernicious malaria with hemoglobinuria" and "erythrolytic hemoglobinuria," the latter being the type most commonly meant by the old terms I reported eight successive cases of pernicious malaria in which hemoglobinuria was demonstrated by the guaiac and turpentine test The degree of hemoglobinuria varied from a mere trace, demonstrable only by the special test, to the intensity of black-water in two cases

It was my idea then that the mechanism of the production of hemoglobinuria in the two types differed I thought that in the first type the preceding hemoglobinemia was brought about by the destruction of innumerable erythrocytes, each by its infecting parasite, the unused hemoglobin being set free in the plasma In the second type, the theory is generally accepted that there is an erythrolysis due to an unknown hemolysin

Since the report was made, I have studied nineteen additional cases of pernicious malaria with reference to hemoglobinuria, making twenty-seven cases in all In twenty-two of these hemoglobinuria was demonstrable In eight instances there were traces only of hemoglobin in the urine, in seven the gross appearance of the urine suggested the probability of hemoglobin, in the other seven cases the hemoglobinuria was of blackwater intensity Four of the five patients without hemoglobinuria were comatose with but few parasites in the peripheral blood; two died and at

*Read at the eighth annual meeting of the American Society of Tropical Medicine, New Orleans, May 18, 1911, being the result of studies in the Colon Hospital, Cristobal, C Z

1 Brem, W V THE ARCHIVES INT MED, 1911, vii, 153

autopsy the brain capillaries were found to be thrombosed and contained numerous parasites, while there were but few in the spleen and bone-marrow The fifth patient had a heavy peripheral infection, about 9 per cent of the corpuscles containing parasites He was very ill, but did not become comatose and no hemoglobin could be demonstrated in his urine

TABLE SHOWING RELATION BETWEEN THE NUMBER OF PARASITES IN THE PERIPHERAL BLOOD AND THE DEGREE OF HEMOGLOBINURIA

	Infected Corpuscles Counted Per Cent Infected	Degree of Hemoglobinuria		Infected Corpuscles Estimated Per Cent Infected	Degree of Hemoglobinuria
1	43	++	15	8 10	0
2	29	+	16	5 10	++
3	23 5	++	17	5-10	+
4	17 6	++	18	5 10	+++
5	15 6	+++	19	5 10	+
6	15 4	+++	20	5 10	+
7	12 6	+++	21	5 10	++
8	11 4	++	22	2 3	+
9	9	+++	23	1- 2 5	0
10	6 2	+	24	1- 2 5	+
11	3 2	+++	25	1- 2 5	0
12	2 3	0	26	1- 2 5	+++
13	2	0	27	1- 2 5	+
14	15 20	+++			

+=Trace, ++=gross appearance of urine suggestive of hemoglobinuria, +++=blackwater

After the discovery that hemoglobinuria was an almost constant phenomenon in pernicious malarial infections, the question at once arose as to whether or not the fact could throw light on the etiology of erythrolytic hemoglobinuria There were two of the cases which were difficult to classify The coma with a moderate malarial infection (2 or 3 per cent of infected corpuscles), and the absence of marked jaundice and vomiting seemed to place them in the pernicious group, while the intensity of the hemoglobinuria (blackwater) suggested the erythrolytic group They were border-line cases and suggested strongly a connection between the two Finally, a case that seemed to be even more of a clinical link occurred The patient was admitted one afternoon, at which time it was found that 9 per cent of his corpuscles were infected with young forms of estivo-autumnal parasites The urine was not hemoglobinous It was estimated that the group of parasites would sporulate during the evening of the following day, and it was thought that then hemoglobin might be demonstrated in the urine The expected paroxysm of fever occurred late in the afternoon, it was accompanied by vomiting, and jaundice rapidly developed, at 9 30 p m the first urine was passed and was found to be typical blackwater, the parasites, which had been numerous all day promptly disappeared and none could be found the following morning The peripheral infection in this case was sufficient to classify it as pernicious, while the paroxysm, which came approximately at the

time calculated from the blood examination, was typical in every respect of erythrolytic hemoglobinuria, and was undoubtedly associated with sporulation of the large group of parasites

Before this time we had had all grades of malarial infections, from mild up to 5 or 6 per cent infections of the erythrocytes, associated with typical erythrolytic hemoglobinuria In many of the most severe cases the parasites were few or absent, while in some of the mildest cases they were numerous In order to see if the same lack of relation between the number of parasites in the peripheral blood and the degree of hemoglobinuria obtained in pernicious malaria with hemoglobinuria, the percentage of infected corpuscles in the pernicious cases was determined and compared with the degree of hemoglobinuria

My original idea was that the degree of hemoglobinuria in pernicious infections would vary with the absolute number of parasites, but as far as can be judged by the peripheral infection, the accompanying table shows that such is not the case The absolute number of parasites may be considered as being equal to the sum of the parasites in the peripheral circulation and the internal organs We know that a scarcity of parasites in the peripheral circulation does not indicate a scarcity in the internal organs, but a heavy peripheral infection does indicate a heavy internal infection Granted that in all the light peripheral infections in the above table there was a heavy internal infection, it seems reasonable to assume that there was a still heavier internal infection associated with the heavy peripheral infections Autopsy findings, also, indicate that this is the case Therefore, for purposes of comparison, the peripheral infection may be considered a rough indicator of the absolute number of parasites If the criterion of infection is valid, it is evident that the hemoglobinuria of pernicious malaria has this in common with that of erythrolytic hemoglobinuria, that the intensity of the hemoglobinuria is not directly related to the absolute number of malarial parasites Further, it seems probable that in some pernicious infections the destruction of corpuscles and the liberation of hemoglobin is not confined to the infected erythrocytes

These facts support the theory that malarial parasites produce an hemolysin that varies in the intensity of its action in different hosts or under different conditions of environment, or that some strains of malarial parasite may elaborate a larger quantity of or an especially powerful, hemolysin That the malarial parasite does generate an hemolysin may be reasonably inferred from the fact that it utilizes the hemoglobin of the infected cell, probably as a food Brown[2] has shown recently that malarial pigment is hematin, and this proves that the parasites or their products have a power to break up hemoglobin He suggests that they possess a proteolytic enzyme Whatever may be the nature of the sub-

2 Brown, W H Jour Exper Med 1911 xiii No 2 p 290

stance it probably acts, first, by dissolving the hemoglobin, which passes into the parasite by osmosis, and is there decomposed into globulin and hematin

I have begun some experiments that so far seem to indicate that malarial organisms do generate an hemolysin In several experiments malarial infected blood was quickly defibrinated while kept at about 37 C. and measured quantities were placed in sterile tubes as follows

Tube 1 Defibrinated blood 0 8 c c
Tube 2 Defibrinated blood 0 8 c c plus 0 2 c c of 0 05 per cent quinin in 0 9 per cent salt solution
Tube 2 Defibrinated blood 0 8 c c plus 0 2 c c of 0 1 per cent quinin in 0 9 per cent salt solution
Tube 4 Defibrinated blood 0 8 c c plus 0 2 c c of 0 025 per cent quinin in 0 9 per cent salt solution

The tubes were incubated for forty-eight hours, during which time they were shaken four times Cultures on agar were then made to exclude contaminating hemophilic organisms The tubes were centrifugalized and readings made, comparing hemolysis with that of controls of normal blood similarly treated The quinin added to Tubes 2, 3, and 4 gave solutions of quinin 1 to 5,000, 1 to 10,000, and 1 to 20,000, respectively, approximating concentrations in the circulating blood when given therapeutically The results, so far, may be summarized as follows

1 Malarial defibrinated blood showed greater hemolysis than the same blood to which quinin had been added, and greater than the controls

2 The quinin tubes showed degrees of hemolysis that varied in proportion to the strength of solution in one experiment, and in another in inverse proportion In the latter instance, the parasites were not as promptly killed by the weaker solutions as they were in the former, and it seemed that parasitic hemolysis was added to quinin hemolysis, thus causing hemolysis to vary inversely as the strength of the quinin solution None of the quinin tubes, however, showed as much hemolysis as the tubes with only defibrinated malarial blood

3 Smears made from the defibrinated blood after incubation showed malarial parasites in various stages of degeneration Many of the original unpigmented forms grew larger and became pigmented before death These larger parasites were invariably found in corpuscles partly or completely hemolyzed The majority of the parasites, however, appeared to have died quickly In the stained specimen they appeared as round blue dots, the chromatin having lost its acidophilic power, and their corpuscles were never hemolyzed In the strongest quinin solutions the parasites seemed to have been killed quickly and no hemolyzed corpuscles containing parasites could be found Crescents retained a fairly normal appearance for forty-eight hours in defibrinated blood, but they were distorted into

bizarre shapes and spherical masses by the quinin, and their staining properties were markedly altered

It may be said that the experiments demonstrate that malarial parasites or their products possess a certain power to hemolyze red corpuscles Only the parasites that underwent some growth in the incubator exhibited this power The experiments are too few to permit further conclusions, but they seem to indicate that quinin in salt solution, added to malarial defibrinated blood in quantities approximating therapeutic strengths, inhibits parasitic growth and parasitic hemolysis, and that the quinin itself produces some hemolysis in forty-eight hours, the hemolysis being of about the same intensity as that in control tubes of non-malarial blood

Similar experiments have been carried out in seven cases of erythrolytic hemoglobinuria The results showed no marked deviation from the normal Corpuscles from different patients seem to vary slightly in their resistance to the quinin solutions

In the seven cases of erythrolytic hemoglobinuria, the serums and corpuscles were tested against normal serums and corpuscles, and with serums and corpuscles of other hemoglobinuric patients In no case has any hemolysin been demonstrated, the results agreeing with those of Barratt and Yorke [3] The hemoglobinuric bloods tested against normal bloods have fallen naturally in the agglutination groups determined by Moss [4]

Group I—2 cases	Group III—0 cases
Group II—1 case	Group IV—4 cases

In certain instances I have found that hemoglobinuric serum possessed atypical agglutinating powers against corpuscles of other hemoglobinuric patients For instance, the serum of Group I normally should not agglutinate corpuscles of any group, and the corpuscles of Group IV should not be agglutinated by any serum But I found that the serum of both of the hemoglobinuric Group I patients agglutinated hemoglobinuric Group IV corpuscles. I do not yet know what significance this may have, but it is interesting to note in connection with it that in two instances I observed in smears from hemoglobinuric patients phagocytosis of red corpuscles Ottenberg observed this latter phenomenon in smears from the blood of patients transfused with blood of donors belonging to another group, the corpuscles of which were agglutinated by the patient's serum. In the hemoglobinuric serum the atypical agglutination of other hemoglobinuric corpuscles and the autophagocytosis of erythrocytes suggest the presence of an agglutinin not present in normal blood Hemolysins

3 Barratt, J O W and Yorke, W Ann Trop Med and Parasit, 1909, iii, No 1, p 1-256

4 Moss, M L Bull Johns Hopkins Hosp 1910, xxi 63

in normal serums have always been found accompanied by agglutinins, but the hemolysins can be destroyed (by destroying the complement) without affecting the agglutinin It seemed possible, therefore, that in hemoglobinuria, the complement might have been absorbed and so the demonstration of an hemolysin prevented But when complement was added to hemoglobinuric serums by adding *serum of a normal person* belonging to the same group no hemolysis occurred The hypothetical hemolysin appeared to have been completely absorbed, or used up during the process of erythrolysis

Three guinea-pigs were inoculated with blood from three patients with erythrolytic hemoglobinuria Two pigs that received 6 and 5 c c of blood died within thirty-six hours The third received 5 c c and appeared ill for about two days, but recovered None voided hemoglobinous urine and the autopsy urine did not yield a positive guaiac and turpentine reaction At autopsy a somewhat greater quantity of bloody fluid was present in the peritoneum than had been injected, but there seemed to be no other lesions A small quantity of heart's blood from each of the two dead pigs was injected into other pigs intraperitoneally They remained unaffected

Finally, one other experiment was made which I hesitate to report because it is open to certain objections, and because it has not been repeated on account of the fact that we have not since had a suitable case As it is, however, the experiment is of such interest that it seems justifiable to present it

The blood of a patient with a very heavy estivo-autumnal malarial infection was laked immediately with sterile distilled water, and the stromata of the corpuscles quickly thrown down with the centrifuge A smear showed that many parasites were thrown down with the stromata The supernatant fluid was removed and the sediment was ground with sterile sand and then was taken up with a small quantity of distilled water, with which it was allowed to remain in contact for some time Then an equal quantity of 1 8 per cent salt solution was added It was thought that an extract of parasites in 0 9 per cent salt solution might be obtained in this way A small quantity of this extract was added to an equal quantity of a 5 per cent suspension of normal corpuscles, and the mixture incubated over night Complete hemolysis took place A platinum loopful of the parasite extract was then added to 0 25 c c of a 5 per cent suspension of normal corpuscles, and again hemolysis was complete after incubation over night A control made with a similar extract of leukocytes showed no hemolysis However, as a transplant from the parasite extract on agar showed the presence of a contaminating bacillus, which had probably produced the hemolysis, I lost interest in the experiment, and put aside the extract in the ice-chest Several days later the extract was tested again against normal corpuscles and no hemolysis was obtained The contaminating organism was still present If

it had caused the hemolysis in the first tests, hemolysis should have occurred, also, in the last As the first culture of the contaminating organism had been saved, it was inoculated into a 5 per cent. suspension of normal corpuscles No hemolysis took place This appears to exclude the possibility that the hemolysis in the first tests was due to the contaminating organism, and since no hemolysis was obtained with leukocytic extract, it seems plausible that the first hemolysis was due to an hemolysin derived from the estivo-autumnal malarial parasites

If this experiment can be repeated, and if an hemolysin in solution can be obtained in considerable quantity from malarial organisms, an interesting field of experiment will be opened, and the question of the relation of malaria to erythrolytic hemoglobinuria should be definitely settled It is probable that such an extract of parasites would in large quantities reproduce the phenomena of the disease in animals, and that in animals an antihemolysin might be stimulated by repeated small doses such as the infected man may receive during the incubation period Quinin may inhibit the development of the antihemolysin Numerous other experiments suggest themselves, a discussion of which at length would be premature

SUMMARY

1 A consideration of pernicious malaria with hemoglobinuria, and the transition cases between it and erythrolytic hemoglobinuria, strongly inclines one to believe that both forms are due directly to an hemolysin produced by the malarial parasite The estivo-autumnal organism is nearly always the one concerned

2 The mechanisms of the production of the two types are, it is thought essentially the same, but differ markedly as a rule, in degree

3 The small amount of experimental evidence so far collected tends to confirm the above views

4 One of two explanations may account for the irregularity and infrequency of hemoglobinuria in malarial infections

A Different strains of parasites may generate hemolysin that varies in quantity or intensity with the strain or with environment that is inimical to the parasites, such as quinin or relative immunity to malaria resulting from previous infections

B An antihemolysin may be formed as a rule, during the incubation period of malarial infections when gradually increasing doses of parasitic hemolysin are presumably being liberated In this case quinin, exhaustion exposure etc., may inhibit the production of antihemolysin, especially in debilitated persons who have suffered from previous malaria In pernicious infections antihemolysin formation may be good but the production of hemolysin by enormous numbers of parasites may be sufficient to more than neutralize it

I wish to thank Col W C Gorgas Chief Sanitary Officer for permission to publish this paper

NOTE.—Since the above paper was written Zeiler and I have obtained two more extracts of parasites from the different pernicious malarial infections The

extracts were made like the one reported above, except that grinding of the sediment with sand was omitted Both of these extracts contained a fairly strong hemolysin Three parts of the extracts hemolyzed completely one part of a 5 per cent suspension of erythrocytes in from twenty minutes to one hour The hemolysin was thermolabile, its action was inhibited by one part of serum from normal persons, from one patient with pernicious malaria (the patient from whom one extract was obtained), and from two patients with erythrolytic hemoglobinuric fever The antihemolysin in these serums was thermostabile The serums were treated with quinin and tested for antihemolytic properties The normal serums were unimpaired, but the serums from erythrolytic hemoglobinuric patients seemed to be weakened by the same quantity of quinin and in one instance hemolysis was complete in one hour The experiments need confirmation and we hope to be able to report more exact quantitative work They seem to reconcile the malarial and quinin views of erythrolytic hemoglobinuria and to connect it definitely with malaria The therapeutic measure of transfusion with normal blood is obviously suggested

423 Security Building

THE RÔLE OF ACIDOSIS OF THE TISSUES AS A FACTOR IN THE PRODUCTION OF AN ATTACK IN PAROXYSMAL HEMOGLOBINURIA*

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During January, 1910, a colored man suffering from paroxysmal hemoglobinuria was admitted to the Cincinnati Hospital He gave a history of passing blood-colored urine, particularly on exposure to cold While producing congestion above the elbow in order to obtain blood from the median vein for a Wassermann determination, it was noticed that at such times there was obtained a blood-serum which was laked. This led me to investigate more closely the effect of carbonic acid gas on the washed corpuscles obtained both from the patient and from a normal individual, and the effect of salts in controlling this hemolysis was also studied This forms a complete report of the work done, and which was briefly referred to by Martin H Fischer[1] in his work on edema

REPORT OF CASE

History—The patient, H C, colored, male, aged 26, single, entered the Cincinnati Hospital Dec 31, 1909, suffering from pains in the back He had had none of the ordinary diseases of childhood, had rheumatism about six years prior to admission, he had returned from the South about one year previously, where he had been for several years While there he had a chill every evening, for which he took quinin Several years ago, he said, he was troubled with gall stones He admitted syphilis and gonorrhea He was not a heavy drinker and denied the use of drugs or of highly seasoned foods

Onset—Patient had been working on the river, where he was exposed to the rough weather, was compelled to labor hard, and perspired Eight days prior to admission the patient began having pains in the left side in the region of the kidney He said that his urine was bloody for several days

Present State—On admission the patient appeared to be a fairly well developed colored man His temperature was 97 6 F The conjunctiva was yellow tinged Chest Inspection Negative Palpation Vocal fremitus increased in right upper lobe Percussion Diminished resonance over right upper lobe Auscultation Prolonged expiration and roughened breathing over right upper lobe Moist rales over the entire lung area Heart Nothing abnormal found Abdomen Pain in left lumbar region X ray showed nothing abnormal about the kidney or ureter

Course—Jan 9, 1910 The patient had intermittent attacks of hemoglobinuria which usually came on in the afternoon During the intervals, the urine was clear Cystoscopic examination showed that the hemoglobinuria was bilateral He was now transferred from the surgical to the medical service Dur-

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*From the Laboratory of the Cincinnati Hospital, Medical Department University of Cincinnati

1 Fischer Martin H Edema p 173 Philadelphia, 1910

ing the next five days he passed bloody urine once On Jan 15, 1910, the blood picture showed as follows

Red cells, 3,200,000, white cells, 7,000, polynuclears, 59 per cent, large lymphocytes, 14 5 per cent, small lymphocytes, 19 0 per cent, eosinophils, 4 0 per cent, transitional, 3 8 per cent

There were no abnormal cells, the red cells were anemic During or immediately after an attack the blood picture seemed to approximate the normal About three days after one attack the count showed polynuclears, 46 0 per cent, lymphocytes, large and small, 50 0 per cent, eosinophils, 4 0 per cent

The temperature would vary from subnormal and normal to 99 2 and 100 2 F On January 29 it reached 104 F, owing to an attack of acute tonsillitis, which quickly subsided and was not accompanied by an attack of hemoglobinuria The fecal examination made Jan 10, 1910, showed a yellow, formed stool, no free fat, a few meat fibers well digested, no parasites Blood culture was negative

The Noguchi deviation of complement test was distinctly positive

The patient improved while in the hospital, the treatment being rest, warmth, light diet Potassium iodid was given internally The attacks became fewer in number, and the patient was discharged Feb 26, 1910 feeling much improved in health

Examination of the Urine—Jan 2, 1910, the urine passed was light amber in color spectroscopic examination was negative, likewise the guaiac, bile and Ehrlich's aldehyd reaction tests

Jan 3, 1910, the urine was black in appearance, the spectroscopic examination gave a double line, one in the green and one in the yellow fields, the guaiac test was positive, the bile test was unsatisfactory and Ehrlich's aldehyd reagent gave a distinct scarlet color in the cold, with the corresponding spectrum

January 5, the urine was smoky in color, the spectroscopic examination was negative, the aldehyd reaction was positive a scarlet color, in the cold Microscopic examination showed the presence of granular casts, no corpuscles and no parasites

January 6, a Bier's congestive bandage was applied to both upper arms over a period of ten minutes In two and one third hours the urine passed was dark and contained albumin Spectroscopic examination showed the presence of hemoglobin, and Ehrlich's aldehyd reaction was positive in the cold January 7, the morning urine was amber in color, spectroscopic examination was negative, no albumin, the aldehyd reaction was positive in the cold The sediment showed casts but no corpuscles

Examination of the Blood-Serum and Corpuscles—January 7, at noon, a congestive bandage was applied and the blood removed from the arm vein A portion of this blood was defibrinated at the bed side and the serum after centrifuging was distinctly laked Another portion was set aside in a sterile test tube and kept at —10 C, and still a third portion was kept at 37 C The blood-serum which separated in both test-tubes was distinctly hemolytic

The blood serum was then examined for the presence of syphilitic antibodies according to the Noguchi modification and a distinct inhibition in hemolysis was obtained The patient's corpuscles were then again obtained, washed three times in normal salt solution and subjected to the action of another syphilitic serum as follows

	Corp Suspension, Drops	Normal Salt Sol, c c	Syphilitic Serum c c (Webb)	Hemolysis
1	1	1	0	—
2	1	1	0 5	—
3	1	1	1 0	—

Since no hemolysis resulted after incubation at 37 C and allowing to stand until the next morning, it was determined to test the action of another syphilitic serum after adding complement

Jan 8 1910, the following tests were made

	Patient's Washed Corpuscles, Drops	Guinea-pig Complement, 40 Per cent c c	Syphilitic Serum, c c (Webb)	Salt Solution c c	Result
1	1	0 1	0 1	1	—
2	1	0 1	0 2	0 8	—
3	1	0 1	0 4	0 6	—
4	1	0 1	0 8	0 2	—

The controls, using the patient's washed corpuscles without added syphilitic serum, also my own washed corpuscles in place of the patient's in the above experiment, were also negative Evidently the syphilitic bodies or antibodies played no great part in the production of the hemolysis

OTHER FACTORS WHICH MAY INDUCE AN ATTACK

The effect of cold in producing an attack of hemoglobinuria was spoken of by the patient himself It was clearly shown above that when a congestive bandage was simply placed on the upper arm at first the blood-serum became laked, and later the urine was colored red and contained hemoglobin It was further found that by simple catheterization, a typical chill was developed, which was later followed by the passing of a highly colored urine containing blood-coloring matter

The increase of temperature associated with the attacks can be readily explained by the action of the liberated hemoglobin on the system Vaughan proved this beautifully in animals when he found that laked blood corpuscles of either man or rabbit after filtration cause an elevation of temperature when injected into rabbits either intra-abdominally or intravenously

HOW IS THE HEMOLYSIS ACCOMPLISHED?

The presence of a specific amboceptor which has to do with causing a solution of the corpuscles *in vivo* is assumed by many authors Donath and Landsteiner[2] were the first to show that in the cooled extremity the patient's corpuscles were acted on by the specific amboceptor and thus prepared, were acted on by the complement in the general circulation leading to hemolysis This was confirmed by later observers[3] Hymans[4] later showed that the blood-serum of hemoglobinuric patients contained specific substances which in the presence of free CO_2 acted on the corpuscles of the patient at lower temperatures (3 to 16 C) leading to their hemolysis They state further that the blood-serum and corpuscles of

2 Donath and Landsteiner Munchen med Wchnschr 1904 li 1590, Meyer Erich and Emmerich E Ueber paroxysmale Hæmoglobinurie Deutsch Arch f klin Med 1909 xcvi 287

3 Czernecki Wien klin Wchnschr 1909 No 42 p 1620 Vaughan V C Cumming J G and Wright J H Ztschr f Immunitæts 1911 ix 473

4 Hymans v d Bergh Blut Untersuchungen uber die Hæmolyse bei der paroxysmale Hæmoglobinurie Berl klin Wchnschr 1909 Nos 27 and 35

a normal individual are not hemolyzed in this manner The Donath-Landsteiner phenomenon was not observed in every case, however Cases of paroxysmal hemoglobinuria are reported in which sufficient cooling of an extremity did not lead to an attack Likewise, attacks have not always been produced by placing a congestive bandage about an extremity This has been explained by some as due to the fact that following one attack the complement has been absorbed and must again be produced in sufficient amount in order to cause hemolysis

Evidently existing theories do not account for the many variations which occur in the blood-stream of patients suffering from paroxysmal hemoglobinuria All observers seem to pay especial attention to the specific amboceptors, to the complement, and a few to the presence of free carbonic acid, but none seems to regard the presence of other dissolved substances, particularly the salts, as playing any important factor With the object of ascertaining the part which the salts play in the phenomenon of hemolysis, the following experiments were undertaken

ACTION OF ACIDS ON THE CORPUSCLES AND SERUM

LACTIC ACID

	Washed Corpuscles Drop	Normal Salt Solution c c	Lactic Acid	Result
1	1	1	1 drop conc sol	Immediate hemolysis and conversion
2	1	1	1 drop (1-10 dil)	Gradual hemolysis
3	1	1	2 drops (1-10 dil)	Hemolysis more rapid
4	1	1	4 drops (1-10 dil)	Hemolysis more rapid

ATMOSPHERE OF CARBON DIOXID

A SERUM

On passing a current of dried CO_2 gas into a test tube containing hemoglobinemic serum, a rapid reduction took place By exposing diluted and undiluted hemoglobinemic serum contained in small Petri dishes, to an atmosphere of dried CO_2 gas, a reduction likewise took place, the rapidity depending on the dilution The controls made by exposing similar serum to the action of air over night, suffered no reduction

B CORPUSCLES IN NORMAL SALT SOLUTION

	Patient's Washed Corpuscles	Normal Salt Solution	Atmosphere of CO_2 Exposure	Result at Room Temperature
1	5 drops (Jan 7, 1910)	5 c c	over night	Complete hemolysis
2	5 drops (Jan 10, 1910)	5 c c	3 hours	Slight hemolysis
3	5 drops (Jan 12, 1910)	5 c c	1 hour	Complete hemolysis

My own corpuscles similarly washed and treated showed no hemolysis in one hour, complete hemolysis by the next morning

Both lactic and carbonic acids cause rapid solution of the corpuscles with reduction, the rapidity depending on the dilution This was to be expected Normal salt solution delayed this action The corpuscles obtained from the patient suffering from paroxysmal hemoglobinuria, seemed to be less resistant to the action of the carbonic acid gas, even in the presence of normal salt solution

C CORPUSCLES IN SODIUM CITRATE SOLUTION

Defibrinated patient's corpuscles were washed three times in 1 5 per cent sodium citrate solution Five drops were added to 5 c c citrate solution and exposed to CO_2 atmosphere for three hours at room temperature They were then taken out and centrifuged No hemolysis had taken place Patient s corpuscles in normal salt solution similarly exposed, showed complete hemolysis Corpuscles similarly treated with sodium citrate solution and normal salt solution, and exposed to room temperature, showed no hemolysis

The experiment was repeated using my own corpuscles and similar results were obtained

The corpuscles both from the patient and myself, after washing in 1 5 per cent sodium citrate solution and exposing to CO_2 atmosphere for three hours, were again washed, suspended in normal salt solution and exposed to CO_2 gas Complete hemolysis resulted in three hours

D CORPUSCLES IN NORMAL SALT SOLUTION AND SODIUM CITRATE SOLUTION, IN CO_2 ATMOSPHERE

	Washed Corpuscles 5 Drops	Normal Salt Solution, c c	Sodium Citrate Solution 1 5 per cent , c c	After 4 hours' Exposure at Room Temperature
1	Patient's	5	0	Complete hemolysis
2	Delaney's	5	0	Complete hemolysis
3	Patient's	1 0	0 5	No hemolysis
4	Delaney's	1 0	0 5	No hemolysis
5	Patient's	1 0	0 75	Trace hemolysis
6	Delaney's	1 0	0 75	No hemolysis
7	Patient's	1 0	1 0	No hemolysis
8	Delaney's	1 0	1 0	No hemolysis

These experiments would tend to show that corpuscles in normal salt water suspension are readily hemolyzed in an atmosphere of CO_2, and that the addition of a slight amount of another neutral salt is sufficient to inhibit this action

E CORPUSCLES PLUS SERUM IN AN ATMOSPHERE OF CO_2

	Washed Corpuscles, 5 Drops	Delaney Serum, c c	Exposure 3 Hours at Room Temperature
1	Patient's	0 3	No hemolysis
2	Delaney's	0 3	No hemolysis

In this case a normal serum was sufficient to prevent the hemolytic action of CO_2 on the corpuscles obtained both from the patient and another normal individual

DEDUCTIONS

In the above experiments it was noticed that the corpuscles of patients suffering from paroxysmal hemoglobinuria were somewhat less resistant to an atmosphere of carbonic acid gas, as compared with corpuscles from a normal individual This difference was not very marked, however The chief difference lies in the blood-serum of the patient

Contrary to the findings of Hymans it was found that normal corpuscles in normal salt water suspension were also, although more slowly hemolyzed in an atmosphere of carbonic acid gas Sodium citrate solution, strength 1 5 per cent was sufficient to prevent hemolysis of both the patient's and normal human corpuscles in an atmosphere of carbonic acid gas at room temperature Apparently the salt concentrations of the blood-serum is the factor which determines whether the

corpuscles shall be hemolyzed or not As shown above, normal serum has sufficient salt dissolved to prevent hemolysis of both the patient's and normal corpuscles in an atmosphere of CO_2 at room temperature

Krokiewicz[5] states that inactivated (55 C) serum from a hemoglobinuric patient no longer hemolyzes the patient's corpuscles in an atmosphere of CO_2, after fresh human serum is added as complement By adding this serum he merely increased the salt concentration of the serum which previously was poor in salts

The paroxysmal attacks have been variously ascribed to the action of cold, congestion and trauma, locally or remotely produced It would appear that changes locally in the tissues must be necessary before a state of hemoglobinemia or hemoglobinuria can be produced In view of the fact that cold, trauma and passive congestion may all lead to an attack, and since the three conditions are associated with the production of an excessive acidity of the tissues, it is not unreasonable to suppose that the organic acids thus formed, play some part directly in the production of the attacks The corpuscles may be less resistant, they may be subject to the action of a specific hemolysin, and yet an additional factor acting locally in the tissues seems necessary for an attack to be produced In the presence of the proper salt concentration the corpuscles are protected against the hemolytic action of any organic acids This naturally suggests the giving of neutral salts as a therapeutic agent, to prevent the onset of attacks in patients suffering from paroxysmal hemoglobinuria

In conclusion I wish to thank Dr E W Mitchell, staff physician, for his kindness in permitting me to report this case, also Prof Martin H Fischer for valuable suggestions

19 West Seventh Street

5 Krokiewicz Wien klin Wchnschr, 1911, xxiv 487

OBSERVATIONS ON THE FLUID CONTENTS OF A CYST OCCUPYING THE EPIGASTRIC REGION OF THE ABDOMEN *

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BOSTON

The observations on the fluid obtained from a cyst, probably pancreatic in origin, which are here reported, seem worthy of record even though no satisfactory explanatory theory of the findings can be advanced by the observer The fluid was obtained at operation from a patient who was admitted to the medical service at the Carney Hospital, March 29, 1911, and whose medical record was as follows·

Patient—Carney Hospital Medical No 2055 Male, aged 42

Family History—Father died of sarcoma Mother died of pneumonia Brother died of bronchitis Sister died in infancy No family history of pulmonary tuberculosis

Previous History—Measles, mumps, pertussis, and scarlet fever in childhood Pneumonia thirteen years ago Gonorrhea twenty-three years ago

Habits—Drinks alcohol to excess, chews tobacco

Present Illness—Fourteen months ago his right leg between the shoe top and knee became swollen Soon after this his abdomen became swollen He was admitted to the Boston City Hospital, where his abdomen was tapped twice in March, 1910, yielding a clear straw-colored fluid He remained at the City Hospital about a month and was discharged feeling fairly well During the following month, April, it was necessary to tap his abdomen again After his abdomen was tapped in April he began to notice a sharp pain in his upper abdomen, which radiated to his left shoulder, and a little later he began to have a constant gnawing pain in his abdomen with occasional sharp exacerbations He lost appetite, and began to lose weight and strength The latter part of November, 1910, he noticed a "lump" which appeared in the upper half of his abdomen, but which disappeared, or as he expressed it, "broke" in January, 1911 Following this the patient vomited once or twice daily for about a month During the time that the "lump" was in his abdomen there was more or less tenderness in this region, he had considerable nausea, and was annoyed by having an uncomfortable full feeling after eating At this time he coughed a good deal, and said that once he raised sputum containing a coffee ground sediment and for four or five days there was red blood in his sputum About the middle of February 1911, another "lump" appeared in his abdomen and this has continued to be present During the past year he has lost 50 pounds in weight, has become very weak, and has worked only at short intervals the total amount of time that he has worked being nine weeks He has lost his appetite, complains of an uncomfortable full feeling in his abdomen says that as soon as he begins to eat his

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*Reported at the meeting of the American Society for the Advancement of Clinical Investigation at Atlantic City May 8 1911

stomach feels very much distended and uncomfortable, and he is able to eat very little, being prevented rather by the sense of fulness than by any actual pain His bowels move regularly, he has no headache, no shortness of breath, no jaundice, no abdominal cramps He has had no edema except the swelling of his right leg, which occurred fourteen months ago, and remained only a short time He gets up once at night to pass urine There is no difficulty in urination His urine appears normal

Physical Examination—A well developed, poorly nourished man lying comfortably in bed, breathing regularly, not rapidly His lips and mucous membranes seem somewhat pale and there are numerous dilated venules on his cheeks and nose His pupils are equal, slightly irregular, react promptly to light and accommodation There is a very slight internal strabismus Ocular movements are normal, no pigmentation of the sclerae Tongue is clean Teeth are in fairly good condition, with rather marked pyorrhea alveolaris Throat is negative In the neck there is visible pulsation in the suprasternal notch Thyroid is not enlarged Numerous cervical lymph glands can be easily palpated, though they are not greatly enlarged The same is true of the axillary lymph glands, and to a less degree of the inguinal The thorax is well formed The right side moves rather more than the left during respiration Percussion over the lungs gives good resonance throughout Voice and breath sounds are normal on auscultation and no râles are heard

Heart—Maximal cardiac impulse is seen and felt just inside the nipple line in the fourth interspace, 4½ inches to the left of the mid-sternal line, and the left border of cardiac dulness corresponds to the position of the apex beat The right border of cardiac dulness is 2¼ inches to the right of the mid sternal line in the fourth space The upper border is at the second interspace The cardiac action is regular, sounds are very distant, except at the base, where the second sounds are loud and strongly accentuated The pulmonic second is louder than the aortic second The percussion note over the upper third of the sternum is distinctly dull, almost to the level of the suprasternal notch, and this dulness extends on each side for about 1½ inches from the mid sternal line The pulses are equal, regular, of small volume and low tension

Abdomen—The upper epigastrium is filled with a bulging tumor mass extending out from under the costal margin down to a point 1½ inches above the umbilicus This mass is rounded, measures 8½ inches transversely, 5½ inches vertically, is symmetrical, smooth, firm and elastic In certain places it is slightly tender It descends slightly with respiration Percussion note over the greater portion of it is flat Inflation of the stomach shows an area of tympany above and to the left of this mass, indicating that the stomach is pushed up and lies largely above the left costal margin Below the mass the entire abdomen is tympanitic, and auscultatory percussion indicates that there is an air containing viscus lying transversely below the mass, probably the transverse colon The edge of the liver can be felt distinctly about an inch below the right costal border, and the upper border of hepatic dulness is at the fifth interspace in the right mammillary line The edge of the spleen cannot be felt Percussion dulness of the spleen extends from the sixth rib in the mid-axillary line to the costal margin No masses are to be palpated in the abdomen with the exception of this one in the epigastrium

Genitals—Normal with the exception of a moderate varicocele on the left side

Extremities—The first and second fingers are missing on the left hand There is no edema of the arms or legs Over the lower half of the right leg there is an extensive superficial scar from an old burn

Reflexes—Knee jerks are normal There is no Babinski's sign, no ankle clonus

Urine—March 30, high color, acid, specific gravity 1,019, very slight trace of albumin, no sugar Sediments show a moderate number of leukocytes and

round cells, rare hyaline and finely granular casts April 1, normal color, acid, specific gravity 1,015, slight trace of albumin, no sugar Sediment shows many leukocytes

Stool—April 2, liquid, dark yellow color, very slightly positive guaiac reaction There is a considerable amount of mucus, many undigested muscle fibers, with no increase in the fat elements

Blood—March 30, hemoglobin 85 per cent , white blood cells, 10,000 per cubic millimeter Stained smear shows no abnormality of the corpuscles

Radiography—An *x*-ray of the thorax shows, corresponding to the area of dulness, a shadow of moderate size occupying the upper anterior mediastinum, interpreted as a slight enlargement of the normal mediastinal shadow possibly brought about by the heart and adjacent tissues being crowded up by the epigastric mass beneath the mediastinum

Operation—A presumptive diagnosis of pancreatic cyst was made, and the patient was transferred to the surgical service April 2 and operated on April 3, 1911 At operation by Dr J T Bottomley, a very large cyst was found adherent to the abdominal parietes and adjacent structures, occupying the epigastric region, with the stomach above and to the left, the transverse colon below Incision showed a moderately thick wall to the cyst, and the cyst to be made up of a large single sack filled with a dark colored, somewhat syrupy fluid With the hand in the cyst it appeared that the cyst extended back to the posterior abdominal wall, and no viscera could be definitely made out back of the cyst The cyst was drained

Course and Recovery—The patient made an uneventful recovery Three weeks after the operation, when the patient had returned to an unrestricted house diet, his urine showed for one day a sugar reaction by the Fehling test This promptly disappeared on reducing somewhat his carbohydrates, and did not subsequently reappear during his stay in the hospital, as shown by the following urine examinations, though his diet was not further restricted

April 9, Sugar 0	April 27, Sugar 0
April 20, Sugar 0	April 28, Sugar 0
April 22, Sugar 0	April 29, Sugar 0
April 25, Sugar +	April 30, Sugar 0
April 26, Sugar 0	May 1, Sugar 0

When last heard from July 15, 1911, the patient was feeling in good condition, and the sinus present on discharge from the hospital had healed

Histologic Examination—A portion of the cyst wall removed at operation was examined This showed a cellular connective tissue structure lined in places with vascular granulation tissue, uncovered by epithelium in numerous blocks of tissue which were examined Outside of the connective tissue was an irregular layer of adipose tissue

Diagnosis—The situation of the cyst, the history of its development, and the character of its contents seem to justify the diagnosis of pancreatic cyst As no epithelium was found lining the cyst, and no pancreatic tissue was found in the cyst wall, it is realized that an absolute diagnosis cannot be made Furthermore, the various tests made with the fluid do not give any definite information as to the origin of the cyst, and yet they will be described as being of considerable interest

Examination of Fluid—Fluid obtained from the cyst cavity was of a dark brownish black color, of a slightly syrupy consistence, contained no sediment and on standing did not clot It was of a faintly alkaline reaction, contained a large amount of albumin, and gave no sugar reaction by the Fehling test It gave a strongly positive guaiac reaction for blood The following tests were made on the fluid

April 4 to 6, 1911 To 20 c c of the fluid was added 5 c c of a chloroform solution of thymol, and in this was placed a two inch tube filled with coagulated egg albumin A second experiment of the same kind was prepared These were placed in the thermostat at 37 5 C temperature and left for forty eight hours The reaction remained alkaline and there was no evidence of digestion of the egg albumin

A portion of the fluid was tested[1] for the presence of trypsin by the method of Gross[2] slightly modified by Spooner as follows The fluid was rendered alkaline with sodium carbonate and filtered through a Büchner funnel One c c of the filtrate was added to solutions of Grübler's casein in 1 1000 sodium carbonate At the end of twenty four hours these solutions were tested for undigested casein by precipitating with 1 per cent acetic acid The tests resulted as follows when 1 per cent acetic acid was added after the mixtures had stood for twenty four hours at 37 5 C

Casein solution 1 200 , very cloudy
Casein solution 1 500 , markedly cloudy
Casein solution 1 800 , markedly cloudy
Casein solution 1 1000, considerable cloudiness
Casein solution 1 1500, considerable cloudiness
Casein solution 1 2000, cloudy
Casein solution 1 3000, cloudy
Casein solution 1 4000, cloudy
Casein solution 1 5000, moderately cloudy
Casein solution 1 6000, moderately cloudy

The cloudiness in these experiments indicates that there had been no digestion and so the tests were negative for the presence of trypsin in the fluid

To 20 c c of the fluid was added 20 c c of a starch paste solution and 5 c c of the chloroform thymol mixture This was placed in the thermostat at 37 5 C At the end of twenty-four hours the fluid remained alkaline in reaction, and it markedly reduced Fehling's solution

The control experiment with the mixture of 20 c c of water 20 c c of starch paste, and 5 c c of chloroform thymol mixture, placed under similar conditions did not reduce Fehling's solution at the end of twenty-four hours

A mixture of 20 c c of fluid, 20 c c of water and 5 c c of chloroform thymol mixture placed in the thermostat at 37 5 C for twenty-four hours did reduce Fehling's solution, though the reduction was less marked than was the case when starch paste was added to the fluid Undiluted fluid treated in the same way for twenty-four hours reduced Fehling's solution

A portion of the fluid was placed in a thermostat at 55 C until evaporated to dryness This precipitate rubbed up in water did not reduce Fehling's solution

The remainder of the fluid was placed in the cold room at a temperature slightly above freezing, and remained there until May 3, 1911 (one month) At the end of this time the fluid still failed to reduce Fehling's solution A portion of the fluid was then boiled (May 3) allowed to cool, and filtered free of precipitate through cotton Twenty c c of the filtrate from the fluid after boiling was added to 20 c c of starch paste, and 5 c c of chloroform thymol mixture, and placed in the thermostat at 37 5 C for twenty-four hours At the end of this time there was a marked reduction of Fehling's solution, whereas a mixture of 20 c c of starch paste and 5 c c of chloroform thymol mixture placed under similar conditions yielded a very slight reduction of Fehling's solution Unboiled fluid with and without starch paste after twenty-four hours' exposure at a temperature of 37 5 C reduced Fehling's solution in the same way as had been the case one month previously

The experiments with the tubes containing coagulated albumin were repeated at this time without digestion being evident A rabbit was killed and mucous

1 I am indebted to Dr Leslie H Spooner for making these tests
2 Gross Deutsch med Wchnschr , 1909, xxxv, 706

membrane scraped from the duodenum was mixed with the fluid and the digestion experiments with coagulated albumin were repeated equally with no resultant digestion

Experiments similar to those carried out at 37 5 C of temperature were repeated at a temperature of 60 C At the end of twenty-four hours at this temperature the fluid still failed to reduce Fehling's solution

Some of the fluid after standing for twenty-four hours at a temperature of 37 5 C was placed in a fermentation tube, yeast was added and the tube placed in the thermostat at 37 5 C After twenty-four hours an abundant formation of gas had taken place Fluid without previous exposure to a temperature of 37 5 C similarly yielded gas after the addition of yeast Controls of water and yeast yielded no gas

July 15, 1911 (three and a half months after the fluid was obtained), a portion of the fluid which had remained in the cold room at a temperature slightly above freezing point had acquired a slightly foul odor and still failed to reduce Fehling's solution A portion of this fluid, to which was added some of the chloroform thymol mixture, was placed in the thermostat at 38 5 C for forty-eight hours, at the end of this time it reduced Fehling's solution slightly After forty-eight hours longer in the thermostat at 37 5 C there was no increase in the reducing power of the fluid for Fehling's solution Another portion was treated with subacetate of lead, followed by animal charcoal to remove the coloring matter In this way a clear fluid was obtained which showed no rotation with the polariscope To this clear fluid was added chloroform thymol mixture, and this was placed in the thermostat at 38 5 C for forty-eight hours At the end of this time the fluid reduced Fehling's solution very slightly, but there was no demonstrable rotation of polarized light The excess of lead now was removed from the fluid by precipitation with dilute sulphuric acid and the fluid, after neutralization with sodium hydrate, was again placed in the thermostat at 37 5 C for forty-eight hours At the end of this time there was no increase in the power of reducing Fehling's solution and no rotation of polarized light

SUMMARY

Fluid was withdrawn from a cyst occupying the epigastric region in a man aged 42, which had developed as follows Twelve months previous to admission in the hospital ascites appeared and a simple ascitic fluid was withdrawn on three occasions during a period of two months Following the tappings a constant, gnawing pain with occasional sharp exacerbations developed in his upper abdomen Four months before admission to the hospital a tumor mass appeared in his upper abdomen, to disappear after a month and a half Five weeks before admission this mass reappeared and persisted On admission there was found a large bulging tumor extending from beneath the ribs to an inch and a half above the umbilicus, elastic, smooth, moving slightly with respiration, apparently a cyst crowding the stomach up and the transverse colon down At operation this was found filled with a slightly viscid fluid, dark brownish-black in color, containing changed blood The wall of the cyst showed granulation tissue and no epithelium

The fluid from the cyst was slightly alkaline, and did not reduce Fehling's solution It gave no trypsin reaction, and did not digest coagulated egg albumin at body temperature, either as it came from the cyst or after the addition of scrapings from the duodenum In the

thermostat at body temperature at the end of twenty-four hours it had acquired the power of reducing Fehling's solution, and previous boiling did not prevent this reducing substance from appearing In the thermostat, however, at 60 C no such reducing substance appeared. The addition of yeast to the fluid caused fermentation with the production of gas Preservation at a temperature slightly above freezing for one month had no appreciable effect on the reactions of the fluid Until the fluid was placed in the thermostat at 37 5 C it still did not reduce Fehling's solution At the end of three and a half months at a temperature slightly above freezing the fluid had acquired a slightly foul odor and still did not reduce Fehling's solution, and now when placed in the thermostat at 37 5 C. there was but a slight production of a reducing substance

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A NEW METHOD OF DETERMINING VENOUS BLOOD-PRESSURE

A ALEXANDER HOWELL, M D
PHILADELPHA

A brief review of the work that has been done in devising methods for measuring venous blood-pressure will illustrate the general principles involved, and make easier the understanding of the new method to be described.

The veins of the hand and forearm have been those on which attention has been chiefly centered With but two exceptions, the end sought has been a means of determining the pressure necessary to cause the collapse of one of these superficial veins The observers have differed mainly, as will be noted, in the way in which this collapse was accomplished and the manner in which the required pressure was measured

A contribution, dealing largely with the theoretical possibilities in the field of venous blood-pressures, was made by Frey[1] in 1902 He went a step further, however, and presented an instrument for the determination of this pressure The instrument, in brief, was so devised as to determine the weight in grams necessary to cause the collapse of a superficial vein While simple and direct in principle it lost its practical value through technical difficulties as well as its failure to lend itself readily to the estimation of fluid pressures

An advance on this empirical procedure was made by von Basch,[2] who was the first to use air-pressure and thus to make possible the estimation directly in centimeters of water The air-pressure was transmitted to the vein by holding over it a glass cylinder, which was in turn connected with a water manometer In this way the pressure necessary to cause the collapse of the vein was measured

The evident fault here was a variable in the force with which the cylinder was held against the skin, a considerable factor when dealing with pressures so low as venous ones are known to be Although again satisfactory results were not forthcoming, the method of approaching the problem was new and opened the way for further development of the same idea, by von Recklinghausen and later by Eyster and Hooker

The elimination of the glass cylinder from the procedure was the

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*From the Medical Dispensary of the University Hospital

1 Frey, A Deutsch Arch f klin Med, 1902, lxxiii, 511

2 von Basch, S Wien med Presse, 1904, No 20, p 962, Arch d sc biol, 1904, Supp xi, 117

advance made by von Recklinghausen [3] He substituted what practically amounted to a rubber cylinder for the glass cylinder of von Basch This was made by cutting openings in the top and bottom of a circular rubber bag The lower opening was placed on the vein, while the upper was closed by a glass plate Air was admitted through an opening in the side and the collapse of the vein was viewed through the glass The pressure required was measured on a water manometer Air-tightness was obtained by covering the skin and the surface of the rubber in contact with the glass with glycerin

The next advance was again along mechanical lines and came with the introduction of the box-frame by Eyster and Hooker [4] This appliance supplanted the glass and rubber cylinders The frame was closed below by a rubber dam, in which an opening was cut, and above by a glass plate In using the apparatus the opening in the rubber dam was placed over a vein, and as the pressure within the box was raised, the collapse of the vein was viewed from above, through the glass The box was held in place by tapes passing around the arm and thus left both hands of the operator free Measurements were in centimeters of water

Oliver [5] and Sewall [6] independently followed out the problem in a different direction While bringing pressure to bear on the superficial veins they did this through the medium of a spring which had been standardized against mercury They hardly seem to have opened as promising a field as the other observers the difficulties usually associated with spring devices suggesting themselves

One of the earliest methods, that of Gaertner,[7] while simplicity itself and useful in many instances, has obvious limitations It consists in raising the arm slowly until the veins on the back of the hand disappear, the height above the heart at which this occurs giving the venous pressure

A method which leaves little to be desired from a scientific standpoint has been described by Moritz and von Tabora [8] Its chief value is in the directness of application The pressure in the median vein is measured by passing a cannula into this vessel The procedure is not unlike the administration of an intravenous injection The pressure in the vein is determined by noting the point below which a column of solution in communication with the vein, will not fall In other words, the pressure which is just insufficient to cause a further passage of fluid from the manometer into the vein, is read, as the fluids within the vein and the

3 von Recklinghausen Arch f exper Path u Pharmakol lv, 463

4 Eyster and Hooker Johns Hopkins Hosp Bull, September, 1908, xix, 274

5 Oliver, G Jour Physiol, 1898, xxii, p xli, 1899, xxiii, p v Jour Balneol and Climat, October, 1903

6 Sewall, H Jour Am Med Assn, 1906, xlvii, 1279

7 Gaertner, G Munchen med Wchnschr, 1904, lxxiv, 2038

8 Moritz and v Tabora Deutsch Arch f klin Med, 1909 1910, xcviii, 475

manometer are in equilibrium at this point, this reading is of course the venous pressure

The scope of such a method must of necessity be limited and will lie chiefly in hospital practice, where patients are well under control and where the aseptic measures employed are above suspicion Moritz and von Tabora examined a large number of cases in this way and feel no fear as to untoward results from the procedure

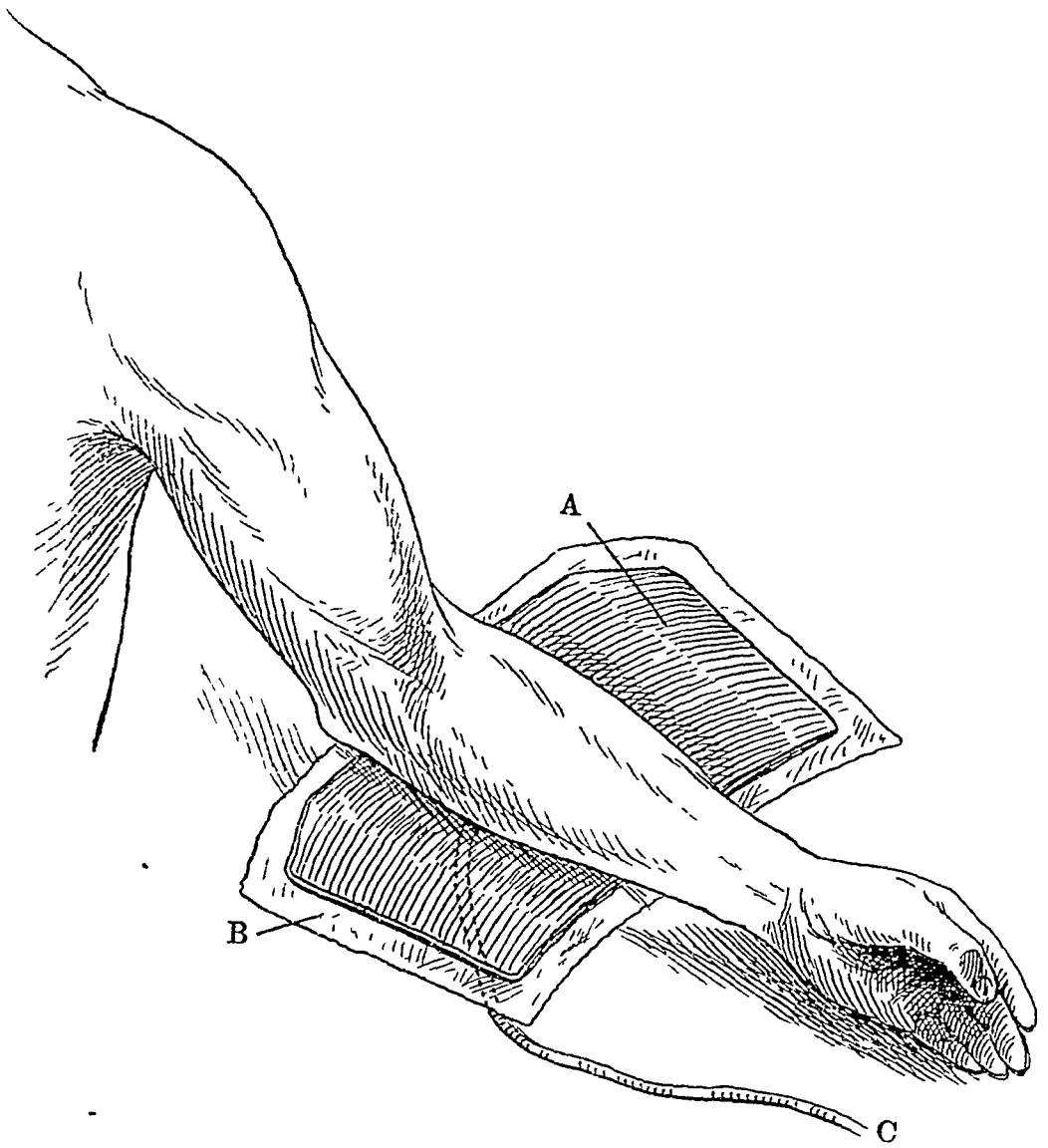

Fig 1 —Lower cuff (rubber bag and covering) before being wrapped around arm A, rubber bag, made of light rubber dam, so shaped that when wrapped around the forearm with its covering B, fits as shown in Figure 2 B, inelastic covering of light material, holding A in place C, rubber tube admitting air to rubber bag A, passing through covering B, as shown at H, Figure 2

As a check to the accuracy of other methods this is the one to be used

To one who interests himself at all in observing the superficial veins it soon becomes evident in what a variable quantity he is dealing The thickness of the skin the amount of subcutaneous tissue and the varying structure of the veins themselves, make a large percentage of individuals

poor subjects for study by any of the above means, except the last described.

A procedure which would be less dependent on these variables and render observation possible on all or nearly all of the veins of a part at once, was the leading thought in the search for a new method The congestion and swelling of the arm, distal to the cuff, as the pressure is dropped below the maximum arterial pressure, in making an ordinary blood-pressure reading, suggested the possibility of utilizing this phenomenon in such a way as to determine the venous pressure The congestion and increase in volume of the arm, below the cuff, being due to the

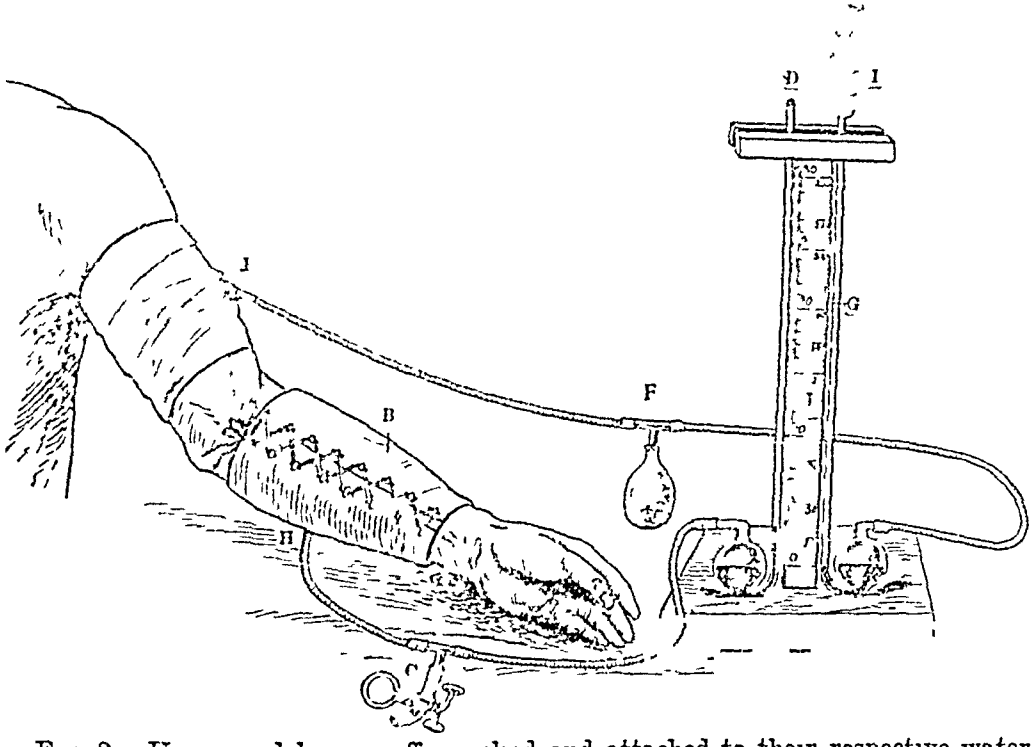

Fig 2.—Upper and lower cuffs applied and attached to their respective water columns E, light cuff for constricting upper arm and obstructing venous return F, glass T and bulb, by means of which pressure is raised in E G, water column measuring pressure in E B, inelastic covering of light material encircling rubber bag C, glass T, side tube and clip, by means of which pressure can be raised in A, Figure 1 D, water column measuring pressure in A (Fig 1)

obstruction of the venous return, while the arterial flow was still in progress, it was obvious that if it were possible to determine the pressure at which this venous obstruction first took place — this would be the venous pressure

A means of constricting the arm, and thus obstructing the venous return, was secured by modifying slightly the usual sphygmomanometer cuff The change consisted in using a lighter rubber bag which was held in place by a few turns of muslin bandage lightly applied The lighter materials are used as they transmit more accurately and quickly the low pressures used in making an observation of this kind

A way to determine the first increase in the volume of the forearm was the real problem to be solved This has been done by devising a special cuff, similar in general to the cuff of the arterial sphygmomanometer, but differing in that it is patterned to fit the tapering forearm and in that it is made of light rubber dam with a light inelastic covering, as diagrammatically represented in Figures 1 and 2

As the arm is constricted at E, by raising the pressure in E F G (Fig 2), a point is reached where the pressure within the cuff just equals and then slightly exceeds that within the veins When this point is reached the veins will collapse and a damming back of the venous blood occurs This manifests itself in an engorgement of the veins below the point of constriction This increase in the volume of the veins, and of the forearm as a whole, is recorded by the system B C D (Fig 2) as follows

Prior to bringing any constricting force to bear at E, a pressure of 3 cm of water is developed in the system B C D (Fig 2) by gently blowing in by mouth at C, until the water column registers the desired pressure The pressure of 3 cm has been arbitrarily chosen, for the inflation of A (Fig 1), as being sufficiently high to overcome the inherent resistance of the cuff to inflation and yet below the probable venous pressure As swelling of the veins in the forearm occurs, following constriction at E, room is made for this increase of volume, within the inelastic covering B (Fig 2), by displacement of a corresponding amount of air from the contained rubber bag A (Fig 1) As this displacement necessitates an increased pressure in the closed system B C D (Fig 2), this increase is registered in the column of water at D The rest of the observation consists in noting the pressure required in the system E F G (Fig 2) to cause this first rise in the water column at D

Directions then for applying and using the apparatus are as follows

1 Apply the special cuff to the forearm, first removing the clip at C, so that all air is forced out of A (Fig 1) when the cuff is laced in place

2 Blow in at C until A (Fig 1) is well filled, readjust the clip at C and let the air slowly escape until the water column D registers 3 cm

3 Apply the upper cuff E, lightly

4 By means of the bulb at F, bring the constricting force to bear at E, by raising the pressure in E F G

5 Note on the scale to the left of J, the pressure in centimeters of water necessary in E F G (Fig 2) to cause the first rise in column D This will be the desired venous pressure

With the expectation of learning something of venous fulness and tone, the pressure has still further been raised in E F G (Fig 2) and

the extent of the rise in column D (Fig 2) noted Rises occurring in column D, under similar pressures in column G, have then been compared

In making a venous blood-pressure estimation, it is necessary, as has been realized by all the workers in this field, to have the vein or veins under observation, at the level of the heart If this is impossible it is then necessary to correct the reading for the force of gravity thus brought into play Levels above the heart decrease and those below the heart correspondingly increase the reading The venous blood-pressure, for example in the forearm or hand hanging at the side is greater than it would be when the forearm or hand is placed at the level of the heart The costal angle, as suggested by von Recklinghausen, has been the point chosen as marking the heart level This landmark is especially appropriate as it localizes the right heart, which is such an important factor in the maintenance of venous blood-pressure

With this instrument the venous blood-pressure has always been taken in conjunction with the arterial pressure This has been made possible without changing to the usual sphygmomanometer by utilizing the "air-water sphygmomanometer," as described by Bendick[9] This consists in closing the upper end of the column G, by screwing down the cap, and raising the water column against the pressure of the enclosed air in the bulb I (Fig 2) In taking the arterial pressure the systolic and diastolic pressures and the auscultatory sequences[10] have been recorded The venous pressure should always be taken before the arterial, as the latter overdistends the veins and renders observations on them, in this condition, undesirable

It is interesting here to note how susceptible the veins are to external stimuli, especially, as has been pointed out by others, to cold and friction As an estimation on the same individual on a warm and a cold day presents differences, it has been found necessary to note the day as warm cool or cold The readings being also influenced by the size of the arm the thickness of the skin and the prominence or obscurity of the superficial veins these facts have been noted In this way it is possible to class individuals in more or less fixed groups presenting similarities in their readings

In the examination by this new method of a series of cases, which could be looked on as normal from a cardiovascular standpoint, the average venous pressure was found to be 7 6 cm of water In this series, the lowest pressure recorded was 4 cm, and the highest 13 cm In the case of the lower reading the patient was a young man with a tentative diagnosis of incipient tuberculosis He had rather a small arm, with

9 Bendick, A J Jour Am Med Assn, June 24, 1911 p 1873

10 Goodman and Howell University Med Bull, November, 1910 p 469 Am Jour Med Sc September 1911

soft moist skin, little subcutaneous tissue and prominent veins, that is, he was an extremely favorable subject for examination by this method. The patient showing the higher reading was a man of 48 years, with a large arm, thick skin, firm subcutaneous tissue and superficial veins which were hardly visible, an individual presenting conditions which would obviously raise the reading. These two cases illustrate what was referred to above, in speaking of the necessity of grouping cases in classes which would present similarities in their readings. In the case of the young man the actual pressure within the veins was closely approximated, while in that of the older man the reading was undoubtedly too high. Since, however, the error is constant for individuals presenting the same physical conditions, allowance can be made for this.

An average has also been taken in a group of cases which showed circulatory disturbance, varying from those of lesser degree to advanced cases in which marked decompensation was present. The average venous pressure in this series was 13.9 cm. of water. The lowest reading of the series was met in a case of well-compensated mitral regurgitation and was 7 cm. The highest was 25.0 cm., in a case of interstitial nephritis showing very high blood-pressure and the signs of chronic uremia. Comparing these results with those of Moritz and von Tabora, obtained by the use of their direct method, it is found that our figures are too high. These observers found the average venous pressure in normal individuals to be 5.2 cm. of water. The lowest reading in their series was 1.1 cm., and the highest 8.7 cm., the former in a case of well-compensated myocarditis and the latter in a patient convalescent from pneumonia.

This comparison shows the average obtained by the new method to be 2.4 cm. higher than it should be. It is evident also that the error is less in the case of the young man who presented favorable circumstances, than in the older one in whom modifying conditions existed.

As one of the chief aids to be derived from the estimation of venous blood-pressures will doubtless be in the following of cases as the patients improve or grow worse, the difficulty under such conditions associated with the correction of readings will be largely eliminated.

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SUBACUTE AND CHRONIC NEPHRITIS AS FOUND IN ONE THOUSAND UNSELECTED NECROPSIES

W OPHULS, M D
SAN FRANCISCO

Ever since Bright, by his admirable papers in 1827[1] and 1836,[2] established the interrelation between renal disease, albuminuria, certain types of dropsy and cardiac hypertrophy the question of a proper classification of the cases which belong to what is commonly known as Bright's disease has been discussed with much interest, and at times with considerable animation, among clinicians and pathologists Bright himself early in the course of his very precise clinical and anatomical investigations, during which he had also noticed in such cases a tendency to inflammations of the serous membranes and to cerebral apoplexy, was struck with the great differences in the gross appearance of the kidneys, and he seems to have favored the view that a subdivision into different groups seemed desirable but he never, according to his published writings, came to any very definite conclusion in regard to this point, although we have Wilks'[3] testimony to the effect that he favored a subdivision into two main groups on an anatomical basis, the one characterized by the development of what is even now described as a "large white kidney" and the other in which, on the contrary, small contracted kidneys were observed at autopsy It would be entirely impossible to trace in a necessarily limited paper the historical development of the subject to the present day, however tempting it might be to do so It may be said, however, in a general way that if all later investigators had followed Bright's shining example by studying and publishing the full facts in regard to their own cases first, before attempting to arrive at any very definite theoretical conclusions, much error and confusion might have been avoided It is naturally somewhat cumbersome to load down one's publications with a detailed recital of the facts observed, still at a later period frequently a few facts well recorded have more value than no end of theoretical considerations, quite apart

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*Read in the Section on Pathology and Physiology of the American Medical Association at its Sixty-Second Annual Session, June 27-30, 1911, Los Angeles, Cal

*From the Pathological Laboratory of Cooper Medical College and of Leland Stanford Jr University

1 Bright Report of Medical Cases, etc, London, 1827

2 Bright Cases and Observations Illust of Renal Disease, etc, Guy's Hosp Rep, 1836, i, 338

3 Wilks Cases of Bright's Disease, Guy's Hosp Rep, 1853, viii, Series 2,

from the fact that they necessarily put some bridle on the scientific imagination of the investigator

We may shortly recall that Toynbee[4] in England, in 1846, and later, in 1851, Reinhardt[5] and Frerichs[6] in Germany attempted to prove that the differences observed by Bright and others merely represented different phases in the same process, a view which in its generality, except as applying to certain cases, has, so far as I can see, been abandoned by all later investigators Wilks,[3] Grainger Stewart,[7] Johnson,[8] and Dickinson[9] in Great Britain, Charcot[10] in France and Bartels[11] in Germany elaborated Bright's original conception of the essential differences between different types of chronic nephritis[12] as the process then began to be called In 1879 Weigert[13] attempted to insist again on the essential unity at least in the histogenesis of the lesions in the kidneys in all cases of Bright's disease, not by reviving the old teaching of the different phases, through which all cases of Bright's disease would pass, but by proclaiming that the one unit which binds all these cases together was the fundamental fact that in all of them there was in the kidneys primary epithelial destruction followed by more or less marked proliferative processes in the connective tissue, and that the differences observed were merely due to differences in intensity, chronicity and interrelation of these two fundamental and interdependent processes His subdivision, based largely on the chronicity of the various changes, so far as they could be determined by histological investigation, does not seem to have proved altogether acceptable to other observers At the present time, among pathologists, especially in Germany there seems to be a tendency to eliminate from the general picture of Bright's disease two conditions which are looked

4 Toynbee The Intimate Structure of the human Kidney, etc, Medico-Chir Tr, 1846, xxix, 303

5 Reinhardt Die Bright'sche Nierenkrankheit, Charité Ann, 1850, i, 194

6 Frerichs Die Bright'sche Nierenkrankheit, Braunschweig, 1851

7 Stewart, Grainger On Bright's Diseases of the Kidney, Ed 2, Edinburgh, 1871

8 Johnson The Minute Anatomy and Pathology of Bright's Disease of the Kidney, Medico-Chir Tr, 1846, xxix, 1, The Inflammatory Diseases of the Kidney, Medico-Chir Tr, 1847, xxx, 165, Certain Points in the Anatomy and Pathology of Bright's Disease of the Kidney, Medico-Chir Tr, 1868, li, 57, Lectures on Bright's Disease, etc, London, 1874, Granular Degeneration of the Kidney, Brit Med Jour, 1875, i, 741

9 Dickinson The Pathology and Relations of Albuminuria, Brit Med Jour, 1876, i, 467, etc

10 Charcot Lectures on Bright's Disease of the Kidney, Translation 1878

11 Bartels The Diffuse Diseases of the Kidneys, Ziemssen's Encyc, 1877, xv, 409, Klinische Studien uber die verschiedenen Formen von chronischer diffuser Nierenentzundung, Samml klin Vortr (Volkmann's), 1871, Int Med, i, 159

12 It is only with such subacute and chronic conditions that we are concerned in this paper

13 Weigert Die Bright'sche Nierenerkrankung, etc, Samml klin Vortr (Volkmann's), 1879, Int Med, ii, 1411

on as more or less purely degenerative in character, namely, amyloid degeneration of the kidneys on the one hand and the very common arteriosclerotic lesions which were so well studied by Ziegler [14] on the other. This tendency is not without its opponents, however, because amyloid degeneration in the kidneys is very frequently associated with what is commonly known as chronic parenchymatous nephritis. Orth says [15] "It is going too far to exclude every large white kidney with amyloid from the inflammatory processes." On the other hand, the differentiation between arteriosclerotic kidneys and what has been described as chronic interstitial nephritis is acknowledged to be a matter of some difficulty.

In 1897, Councilman[16] in our country published an excellent paper which he calls a study of acute diffuse nephritis but in which he also treats of subacute and chronic conditions, and on the basis of which he arrives at the following classification of the subacute and chronic cases:

Subacute glomerular nephritis
Chronic diffuse nephritis—
- A. Chronic glomerular nephritis
- B. Chronic arteriosclerotic nephritis
- C. Chronic degenerative and interstitial nephritis

Senile nephritis

Subacute and chronic glomerular nephritis represent the majority of large white and variegated kidneys, chronic arteriosclerotic nephritis accounts for the majority of contracted kidneys. In 1906, Councilman[17] reviewed his former work and came to the conclusion "It is not probable that much light will be thrown on the numerous obscure questions relating to nephritis by anatomic investigation," and he emphasized the necessity of commencing all over again, so to speak, with a very thorough intensive study of individual cases by pathologists and clinicians conjointly. Jores'[18] important work seems to have emphasized the differences between chronic parenchymatous and chronic interstitial (arteriosclerotic) nephritis, and Lohlein's[19] recent careful clinical and anatomical investigations on glomerulonephritis seem to have brought out this impor-

14. Ziegler: Ueber die Ursachen der Nierenschrumpfung, Deutsch. Arch. f. klin. Med., 1880, xxv, 586.

15. "Man geht zu weit, wenn man ohne weiteres jede grosse weisse Niere mit Amyloid von den eigentlichen entzündlichen Prozessen ausschliessen will."—Orth: Pathol. Anat., 1893, ii, 79.

16. Councilman: Anatomical and Bacteriological Study of Acute Diffuse Nephritis, Am. Jour. Med. Sc., 1897, cxiv, 23.

17. Councilman: The Pathology of the Kidney, Jour. Am. Med. Assn., 1906, xlv, 81.

18. Jores: Ueber die Arteriosklerose der kleinen Organarterien, etc., Virchows Arch. f. path. Anat., 1904, clxxviii, 367; Ueber Arterienveränderungen bei Nephritikern, Verhandl. deutsch. path. Gesellsch., 1904, viii, 174.

19. Lohlein: Ueber die entz. Veränderungen der Glomeruli, etc., Arb. Path. Inst., Leipsic, 1907, No. 4.

tant point that the transition of chronic parenchymatous nephritis into secondary contracted kidney does not seem, from clinical and anatomical evidence, to be so rare as was formerly believed

It may be stated then that the tendency at present is to divide fairly strictly subacute and chronic parenchymatous or glomerulonephritis from what, for want of a better non-prejudicial term, we may call primary contracted kidney The relation of the former to amyloid kidneys does not seem to be entirely clear, nor the relation of the latter to arteriosclerotic kidneys, although many believe that arteriosclerosis is a very important factor in its production It is also pretty generally accepted at the present time that chronic parenchymatous nephritis may develop into secondary contracted kidney and, according to last reports, not so very rarely Exact data on this latter point are not available

It must be acknowledged, however, that many clinicians are not at all satisfied with any of the anatomical classifications so far offered As early as 1880, Greenfield[20] insists that in chronic nephritis no strict subdivision is possible A most interesting example of this point of view we find in Brault, who, in 1884,[21] in perhaps the most admirable exact anatomical treatise on renal diseases, in collaboration with Cornil, developed a most elaborate anatomical classification of nephritis and who, in 1897,[22] insists that the present anatomical classifications of Bright's disease are unsatisfactory He says "The anatomical forms vary according to the intensity. the duration and the character of the irritation The most natural classification is that based on the etiology"[22]

Both Leyden[23] and Muller,[24] two of the foremost clinicians of Germany, voice the same opinion by pointing out that the diagnosis of anatomical conditions cannot be the chief aim of the clinician, and Muller proceeds to a most interesting attempt at an etiological classification which throws a flood of light on individual conditions but which, as a whole, is hardly entirely satisfactory Herrick,[25] in Osler's "Modern Medicine," in 1909, puts great emphasis on the point that no sharp clinical or anatomical subdivision of cases of chronic nephritis is possible or desirable and then gives one of the usual anatomical classifications in lieu of something better

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20 Greenfield Granular Contr Kidney, Tr Path Soc London, 1880, xxxi, 157

21 Cornil and Brault Etudes sur la pathologie du rein, Paris, 1884

22 Brault Classification clinique des nephritides, la Presse méd, 1897, v, 72, Les formes anatomiques varient suivant l'intensité, la durée, la qualité de l'irritation" "La classification la plus naturelle devrait être basée sur l'étiologie"

23 Leyden Ueber Nierenschrumpfung u Nierensklerose, Ztschr f klin Med, 1881, ii, 133

24 Muller Morbus Brightii, Verhandl d deutsch path Gesellsch, 1905, ix, 64

25 Herrick Nephritis, Osler's Modern Medicine, 1909, vi, 103

Being interested in the study of experimental chronic nephritis, it seemed to me necessary to obtain first a thorough understanding of the conditions as they occur in man, and with this object in view I began to study my own material Nothing new could be expected from a study of selected cases, but there was some hope that the natural interrelation of the various types with one another, and with associated conditions such as arteriosclerosis or amyloid, would be brought out more clearly by a complete study of a considerable series of consecutive cases embracing all conditions, with a special view to whatever renal, arterial or cardiac lesions might be present It was to be expected that such an examination would at least show whether any of the known schemes of classification were sufficiently comprehensive to include all cases which were actually observed or whether, indeed, the different types merged into another imperceptibly as is maintained by some, or whether it is possible to find fairly clear lines of subdivision

One thousand consecutive cases seemed a sufficient number to exclude gross error from chance, yet a number not too large to allow a sufficiently intensive study and of proper handling of the material A large majority of the necropsies used in the preparation of this paper were performed by myself personally, and microscopic sections from the most important organs of all cases were seen by me at the time Whatever statistical material has been obtained in this manner can therefore be vouched for as being accurate, except where differences in interpretation are possible, which will be noted in its proper place The last 200 cases were studied especially carefully with the particular object of this paper in mind, and many of the former cases were restudied thoroughly from preserved material, whenever it seemed at all desirable to do so

The study of these cases was approached without any particular object in view and I hope, therefore, with a mind free from all bias so far as it is possible I was frequently somewhat surprised at the results obtained and most particularly when, in the end, a complete subdivision of all cases into fairly distinct groups resulted, without any special effort in this direction

The material studied was such as is found commonly in any large public hospital The following data from the last 200 cases will perhaps give a more accurate idea There were nineteen children and young adults to 20 years of age, 148 adult males and thirty-two adult females Among both males and females, the larger number were between 40 and 60 years of age The chief diseases encountered in these last 200 cases were as follows Manifest tuberculosis 26 5 per cent, severe arteriosclerosis 14 per cent, malignant tumors 9 5 per cent, pneumonia 8 per cent, endocarditis 7 5 per cent, evident syphilis 3 5 per cent, cirrhosis 3 per cent, chronic sepsis 2 5 per cent, and so forth The percentages

are not unusual, except the very high percentage of severe arteriosclerosis which became evident on a close study of the individual cases only

It is a well-known fact that entirely normal kidneys are found very rarely, especially in the later years of life It became necessary, therefore, to establish how far it was possible to eliminate such minor changes from consideration It might very well have been that just such more or less initial still undeveloped lesions could have thrown much light on the histogenesis of the more advanced cases, in fact, the clew to the whole situation might have been just there A very careful gross and microscopic study was therefore made of the last 200 kidneys, which confirmed the general impression that these lesions are practically all of arteriosclerotic origin and that they do not help in elucidating any phase of our subject, except in so far as its relation to arteriosclerosis is concerned A more detailed exposition of this part of the subject follows later In regard to their occurrence according to age and sex, see Table 1

It is interesting to note at this point that, on the whole, general arteriosclerotic lesions develop coincidently with arteriosclerotic lesions in the kidneys, but that there is no strict interdependence between the two processes, a fact, however, well established in medical literature (See Table 2)

The next question which naturally presented itself was whether it is possible to distinguish histologically or otherwise between these common, evidently arteriosclerotic, lesions and the severer lesions which are commonly described as "chronic interstitial nephritis," and which are said to produce the "genuine or primary contracted kidney," whether, as has been said so often, the kidneys of arteriosclerotics were different from severe nephritis with arteriosclerosis In spite of some personal inclination toward the latter view, I have been unable to find any evidence to substantiate it Histologically, the lesions are absolutely identical The process evidently commences in the arterioles, the lesions in which have been especially well described by Jores[18] and his pupils The glomeruli next become involved The lesions in them are also well known and have been made the subject of special study by Thoma,[26] Tschistowitsch,[27] Josué and Alexandrescu,[28] Herxheimer,[29] and others Initial stages of the process, contrary to the belief of some, are fairly frequently seen when one looks over many such specimens They consist in the shrinkage of the glomerulus and a dense fibrous thickening of the capsule as shown

26 Thoma Zur Kenntnis der Circulationsstorung in den Nieren bei chronisch interstitieller Nephritis, Virchows Arch f path Anat, 1877, lxxi, 42, 227

27 Tschistowitsch Die Verodung und hyaline Entartung der Malpighischen Korperchen der Niere, Virchows Arch f path Anat, 1903, clxxi, 243

28 Josué and Alexandrescu Contribution a l'étude de l'artériosclérose du rein, Arch de méd exp et d'anat path, 1907, Series 1, xix, 1

29 Herxheimer Ueber die sogenannte hyaline Degeneration der Glomeruli der Niere, Beitr z path Anat u z allg Path, 1909, xlv, 253

in Figure 1 This thickening in the beginning is fairly cellular The glomerulus at this stage still contains some blood and the nuclei stain well Eventually the glomerulus collapses entirely, loses all nuclear staining and is surrounded by a thick mass of dense hyaline fibrous tissue Even then the remnant of the glomerulus and the capsular hyalin around it stain entirely differently with the Van Gieson method The change has usually been interpreted in this way that as a result of the disease of the arterioles the blood-supply would be cut off from the glomerulus, which then was followed by its collapse, which in its turn would provoke the fibrous thickening of the capsule I have the impression rather that this is only partly true and that the capsular thickening

Fig 1—90× XII 75 Initial stage of glomerular lesions in arteriosclerosis

to some extent must be attributed to the extension of the proliferative process in the arterioles to the capsule

The collapse of the tubules and the proliferation of the interstitial tissue which accompany this change in the glomeruli is also too well known to need further mention I may say, however, that here again I cannot quite accept the idea of those who believe that the process is purely degenerative in character In many instances, as Ziegler[14] himself, who is otherwise responsible for the opposite view, has observed, evidences of a certain degree of inflammation are quite well marked The cellular

infiltration which occurs in such cases is especially well shown in Figures 2 and 4, of which one represents an ordinary arteriosclerotic scar, the other an advanced degree of renal destruction by a similar process, and even in those cases in which it is missing, this may be due to the fact that the process has come to a standstill, which it undoubtedly does eventually in the majority of cases Another fact which to my mind makes it impossible to accept altogether the view that the glomerular lesions are entirely primary and the collapse of the tubules and the proliferation of the connective tissue secondary, is this that in some instances the number of affected glomeruli is much too small to account for the extensive lesions in tubules and connective tissue

TABLE 1—SHOWING DISTRIBUTION OF ARTERIOSCLEROTIC LESIONS ACCORDING TO AGE AND SEX

	1-20	20-40 Yrs		40-60 Yrs		Over 60 Yrs	
Kidneys	Yrs	M	F	M	F	M	F
Free from scars	18	7	4	6	2	1	0
Small scars	1	20	7	47	9	24	1
Large scars	0	2	1	10	4	15	1
Arteriosclerotic nephritis	0	2	0	4	1	6	0
Other renal lesions	0	4	1	1	1	0	0
Totals	19	35	13	68	17	46	2

TABLE 2—SHOWING RELATION OF ARTERIOSCLEROTIC RENAL LESIONS TO GENERAL ARTERIOSCLEROSIS AND TO CARDIAC HYPERTROPHY IN 200 CASES

	Blood-Vessels Elsewhere			
Kidneys	Normal	Slight	Moderate	Marked
			General Arteriosclerosis	
Without scars	31	6	1	0
With small scars	23	52	19 1 with cardiac hypertrophy	14 6 with cardiac hypertrophy
With large scars	5	13	8	7 3 with cardiac hypertrophy
With arteriosclerotic nephritis	0	2 1 with cardiac hypertrophy	4 4 with cardiac hypertrophy	8 8 with cardiac hypertrophy

Casts are very commonly observed in the tubules in the affected areas probably on account of the stagnation of secretion I cannot find any evidence, however, that they have any important relation to the lesions as a whole, as has been suggested by Aufrecht, in 1894,[30] and later by Ponfick [31]

In regard to the formation of cysts (glomerular and epithelial) in such lesions, one factor has hardly received sufficient attention in their production, namely, the shrinkage of the adjoining tissues I am inclined to believe that this is quite important because of the frequent association

30 Aufrecht Zum Nachweiss zweier Nephritisarten, Deutsch Arch f klin Med, 1894, liii, 531

31 Ponfick Ueber Morbus Brightii Verhandl deutsch path Gesellsch, 1905, ix, 49

with it of a sinuous dilatation of the capillaries in the same areas which hardly admits of any other interpretation Beer[32] has called particular attention to the frequency of cystic dilatation of the glomeruli in such cases as shown in my Figure 4, and from my experience I am certain that these cysts cannot all be explained as of congenital origin as suggested by Aschoff

Figures 1 2, 3 and 4 I hope will illustrate sufficiently what type of process I believe to belong to this class and I may say again that, besides the mechanical moment of interference with the circulation which

Fig 2—Oc VIII 45 Large arteriosclerotic scar with considerable cellular infiltration

undoubtedly is important, the evidences of an accompanying low grade of inflammation should not be overlooked

The distribution of the process varies very much in different cases, sometimes one finds many small foci scattered fairly regularly through the renal tissue, at other times one finds a very irregular distribution with the formation of the well-known irregular large purple scars The rest

32 Beer Occurrence of Cystic Changes in the Malpighian Bodies, etc, Am Jour Med Sc, 1904

of the renal tissue may be entirely normal, but in the most advanced cases severe parenchymatous lesions are very frequently associated with it, the character of the lesions is, however, somewhat different from those which one observes in subacute and chronic parenchymatous nephritis In many cases they are probably more or less terminal

Early in the progress of my studies it became evident that this type of renal lesion could not be properly understood unless it was considered in conjunction with all other cases of well-developed arteriosclerosis, which were accordingly tabulated with the following gross result

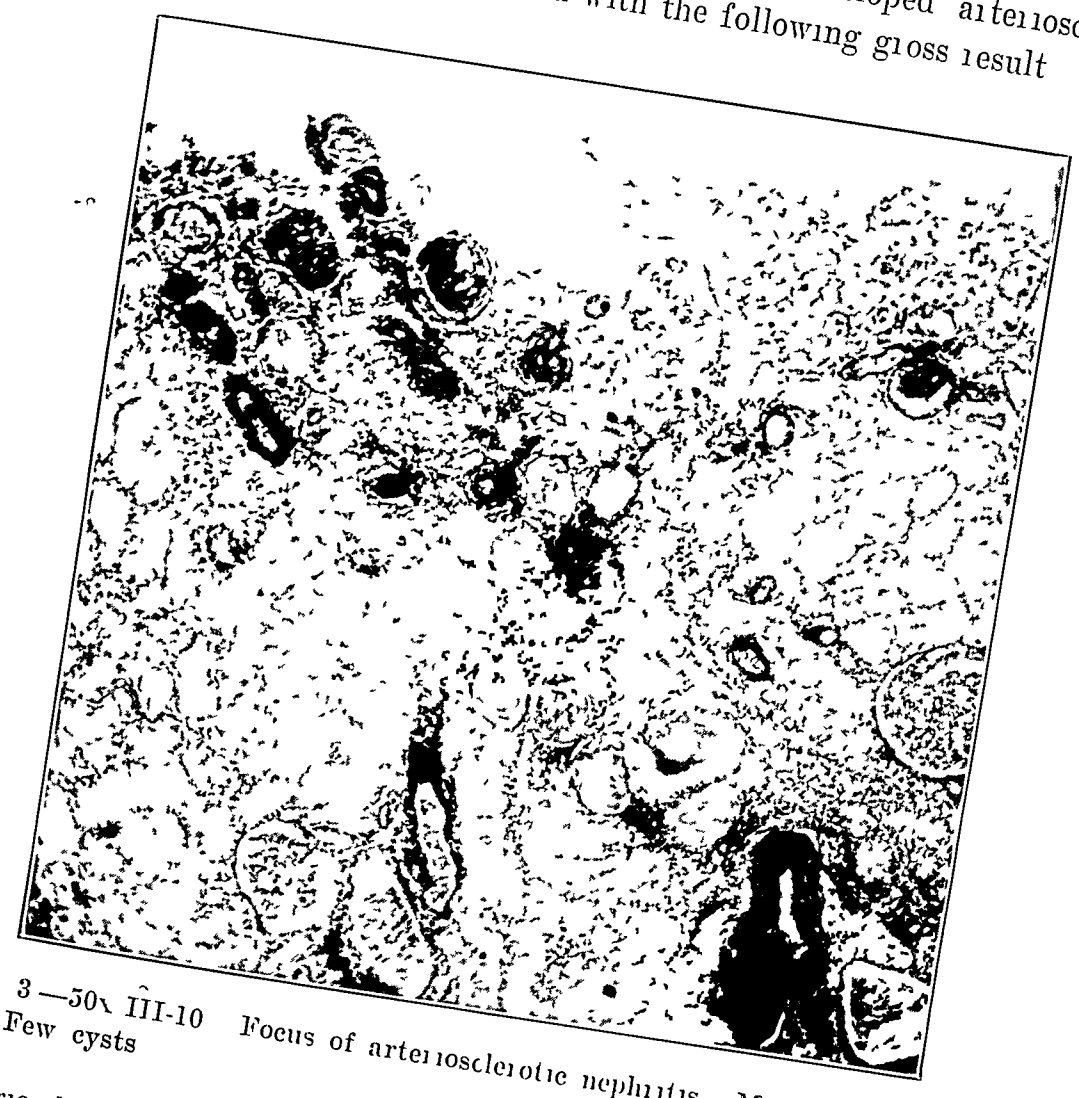

Fig 3 —50× III-10 Focus of arteriosclerotic nephritis Many hyaline glomeruli Few cysts

Arteriosclerosis with valvular disease, 15 cases
Marked arteriosclerosis without cardiac hypertrophy or severe renal lesions, 58 cases
Marked arteriosclerosis with cardiac hypertrophy
with slight renal lesions, 46 cases
with severe renal lesions, 19 cases
Arteriosclerotic nephritis
with cardiac hypertrophy, 25 cases
without cardiac hypertrophy 1 case

TABLE 3.—ARTERIOSCLEROSIS, CARDIAC HYPERTROPHY, SLIGHT

The gross appearance of these kidneys is either entirely unchanged or they show some slight some larger purple scars either at the poles or along the convexity. The cortex may appear some degenerative changes

Number	General Condition	Aorta	Peripheral Art
1 II-6	Strong man of 45	Marked atheroma	Moderate arteriosclerosis
2 III-7	Man of 68	Very marked atheroma	Little arteriosclerosis
3 I 37	Man of 61	Local atheroma of arch, aneurysm	Little arteriosclerosis
4 VII 90	Emaciated old man	Marked atheroma	Little arteriosclerosis
5 VIII 66	Emaciated man of 65	Marked atheroma	Moderate arteriosclerosis
6 III 50	Mod strong man of 65	Very marked atheroma	Moderate arteriosclerosis
7 VII-30	Strong man of middle age	Marked atheroma, aneurysm of arch	Little arteriosclerosis
8 I 66	Strong man of 55	Marked atheroma	Marked arteriosclerosis
9 XIII-101	Mod strong man of 45	Moderate atheroma	Moderate arteriosclerosis
10 XII-71	Poorly nourished man of 65	Marked atheroma	Marked arteriosclerosis, scars in heart muscle
11 XII 62	Strong man of 52	Moderate atheroma	Marked arteriosclerosis, scars in left ventricle
12 VII 20	Strong old man	Moderate atheroma	Marked arteriosclerosis
13 VIII-12	Strong man of 60	Moderate atheroma	Very marked arteriosclerosis
14 XIII-112	Strong man of 45	Moderate atheroma	Marked arteriosclerosis
15 VI 6	Poorly nourished old man	Very marked atheroma	Marked arteriosclerosis
16 III 69	Strong man of 59	Marked atheroma, aneurysm of arch	Moderate arteriosclerosis
17 VI-17	Strong, stout man of 76	Very marked atheroma	Moderate arteriosclerosis
18 VIII 79	Emaciated old man	Marked atheroma	Marked arteriosclerosis scars in heart muscle
19 III 55	Strong old man	Very marked atheroma	Marked arteriosclerosis
20 VI 83	Stout man of 61	Slight atheroma	Marked arteriosclerosis, anemic necrosis of left ventricle
21 VII 74	Emaciated old man	Marked atheroma, aneurysm of arch	Marked arteriosclerosis, few scars in left ventricle
22 IV 113	Strong man of 70	Very marked atheroma	Moderate arteriosclerosis
23 IX 78	Poorly nourished old man	Marked local atheroma, small aneurysm	Marked arteriosclerosis, large scars in left ventricle
24 VII 43	Mod strong man of 65	Moderate atheroma	Marked arteriosclerosis
25 VIII 66	Mod strong man of 67	Moderate atheroma	Marked arteriosclerosis, scars in heart muscle
26 XII 75	Stout woman of 45	Marked atheroma	Marked arteriosclerosis
27 I-15	Poorly nourished man	Marked atheroma	Marked arteriosclerosis
28 I 75	Strong old man	Marked atheroma	Marked arteriosclerosis, gastric ulcer, scar in left ventricle
29 II-7	Strong, stout old man	Marked atheroma	Marked arteriosclerosis, scars in heart muscle
30 II 29	No data	Marked atheroma	Moderate arteriosclerosis
31 III 33	Stout man of 53, painter	Moderate atheroma	Marked arteriosclerosis
32 III 34	Stout woman of 67	Very marked atheroma	Marked arteriosclerosis
33 III 118	Strong man of 49	Slight atheroma	Slight gen arteriosc, aneurysm of right thyroid art, thrombosis of anonyma and right carotid arteries
34 IV 33	Strong man of 50	Very marked local atheroma, aneur of arch	Marked arteriosclerosis
35 IV 34	Strong man of middle age	Marked atheroma	Marked arteriosclerosis
36 IX 72	Strong old negro	Moderate atheroma	Marked arteriosclerosis
37 XII-53	Strong man of 49, painter	Marked atheroma	Marked arteriosclerosis
38 XII 79	Strong woman of 42	Very marked local atheroma aneur of arch	Marked arteriosclerosis
39 IV 10	Fairly strong man of 60	Marked atheroma	Slight arteriosclerosis
40 VI 48	Strong man of 70	Moderate atheroma	Moderate arteriosclerosis
41 VIII 62	Stout man of 55	Slight atheroma	Moderate arteriosclerosis
42 IX 14	Emaciated man of 62	Slight atheroma	Mod arteriosc obst of coronary artery, necrosis of wall of left ventricle
43 XIII-107	Strong man of 55	Marked atheroma	Marked arteriosclerosis
44 IV-78	Strong old man	Slight atheroma	Marked arteriosclerosis
45 VII-12	Strong man of 65	Moderate atheroma	Marked arteriosclerosis, scars in heart
46 III 99	Strong man of 41	Very marked atheroma	Moderate arteriosclerosis

adhesion of the capsule, a slightly granular surface especially along the convexity There may be what reduced and indurated The epithelium may be entirely normal or may show various terminal

Heart	Condition of General Circulation	Other Important Lesions
Slightly enlarged	Good	Pneumonia
Slightly enlarged	Good	Dysentery
Slight hypertrophy of left ventricle	Good	Syphilis
Slight hypertrophy of left ventricle	Good	Infection of urinary tract
Slight hypertrophy of left ventricle	Good	Sarcoma of stomach
Slight hypertrophy of left ventricle	Good	Old apoplexy
Slight dilat and hypertr left ventricle	Beginning disturbance	
Slight hypertr and dilat both ventricles	Beginning disturbance	Pneumonia
Slight hypertr and dilat of both sides	Beginning disturbance	
Mod hypertr and dilat of both sides	Marked chron disturbance	
Some hypertr and dilat of both sides	Marked chron disturbance	
Mod concentric hypertr of left ventricle	Good	Cerebral hemorrhage
Marked concentric hypertr left ventricle	Slight chronic disturbance	Cerebral softening
Marked concentric hypertr left ventricle	Good	Cerebral softening
Marked concentric hypertr left ventricle	Good	Chronic volvulus, gouty deposits in kidneys
1½ times normal, marked hypertrophy of left ventricle	Good	
1½ times normal	Good	Emphysema, gouty deposits in kidneys
1½ times normal, hypertr left ventricle	Marked chron disturbance	
1½ times normal, mostly hypertrophy of left ventricle	Marked chron disturbance	
1½ times normal, mostly hypertrophy of left ventricle	Marked chron disturbance	Gouty deposits in kidneys
1½ times normal, mostly hypertrophy of left ventricle	Little disturbance	Carcinoma of stomach
1½ times normal, mostly hypertrophy of left ventricle	Marked recent disturbance	
1½ times normal, dilatation and hypertrophy on both sides	Begin chronic disturbance	
1½ times normal, mostly hypertrophy of left ventricle	Begin chronic disturbance	
1½-2 times normal, marked hypertrophy and dilatation of entire heart	Marked recent disturbance	
18x12 cm marked hypertrophy and dilatation of entire heart	Marked chron disturbance	
2 times normal, hypertrophy and dilatation of both sides	Marked chron disturbance	Chronic cholecystitis
2 times normal, hypertrophy and dilatation of entire heart	Good	Cholelithiasis and suppurative cholecystitis
2 times normal, hypertrophy and dilatation of entire heart	Marked chron disturbance	
Marked hypertr and dilat entire heart	Marked chron disturbance	Syphilis
2 times normal, hypertrophy and dilatation of all cav	Marked chron disturbance	Cerebral softening
Marked hypertr and dilat entire heart	Good	Fracture of neck of femur
2 × normal, marked hypertrophy and dilatation of entire heart	Marked chron disturbance	
2 × normal, marked hypertrophy and dilatation of entire heart	Marked recent disturbance	Syphilis
2 × normal, marked hypertrophy and dilatation of entire heart	Marked chron disturbance	
2 × normal, marked hypertrophy and dilatation of entire heart	Good	Chronic suppuration in urinary tract
2 × normal, marked hypertrophy and dilatation of entire heart	Mod chronic disturbance	Septic endocarditis, emphysema, peritonitis
20 × 15 cm hypertrophy and dilatation of entire heart	Marked chron disturbance	
2 3 × normal, marked hypertrophy and dilatation of entire heart	Marked chron disturbance	
2-3 × normal, marked hypertrophy and dilatation of entire heart	Marked chron disturbance	
2 3 × normal, marked hypertrophy and dilatation of entire heart	Marked chron disturbance	
2-3 × normal, dilatation and hypertrophy, largely heart	Marked chron disturbance	
2 3 × normal, hypertrophy and dilatation of both sides	Marked chron disturbance	
3 × normal	Marked chron disturbance	
5 × normal, marked hypertrophy and dilatation of entire heart	Marked chron disturbance	
5 × normal, marked hypertrophy and dilatation of entire heart	Marked chron disturbance	

The dividing line between marked arteriosclerosis with severe renal lesions and what I have termed "arteriosclerotic nephritis" is purely arbitrary in fact many cases which on more careful examination proved to be cases of general arteriosclerosis with comparatively insignificant renal lesions were diagnosticated at the autopsy table as "chronic interstitial nephritis' with cardiac hypertrophy, etc., under the mistaken assumption that the renal lesion was the most important phenomenon I believe that this mistake is made quite commonly and that in many of these cases clinically and anatomically too much emphasis is placed on the condition of the kidneys

The abstract of cases of marked arteriosclerosis without hypertrophy and Tables 3 4 and 5 give the most important details in regard to these

TABLE 4.—ARTERIOSCLEROSIS, CARDIAC HYPERTROPHY, MODERATELY EXTENSIVE LESION IN KIDNEYS ARRANGED ACCORDING TO SIZE OF HEART

The kidneys of this series show much more advanced lesions The capsule is usually more or less adherent, although in some cases it strips remarkably well The kidneys are all distinctly reduced in size The smallest one (IV 51) measures 10×5×3 cm The surface shows two types of lesion, either it is finely granular or it shows large irregular, retracted scars Frequently these two conditions are combined The retracted parts are always of a dark purple color very hard, the tissue in between gray, or opaque and yellowish when there is much granular and fatty degeneration On the cut surface the cortex is found considerably reduced, more especially so in those places where there are large scars on the surface The markings on the cut surface are often more or less indefinite The lesions, in short, are such as are commonly described as those of a moderately advanced interstitial nephritis with or without associated parenchymatous degeneration and, in fact, this was the diagnosis made in the majority of cases at the post mortem table

Number	General Condition	Aorta	Peripheral Art
1 II 21	Poorly nourished man	Marked atheroma	Mod arteriosclerosis
2 IV 40	Strong man of 66, clerk in winery	No atheroma	Mod arteriosclerosis
3 VI 101	Emaciated old man	Slight atheroma	Mod arteriosclerosis
4 VII-107	Strong man of 60	Marked atheroma	Marked arteriosclerosis
5 XII 61	Strong man of 60	Slight atheroma	Mod arteriosclerosis
6 V-10	Strong man of 67	Moderate atheroma	Marked arteriosclerosis
7 IX 76	Strong man of 60	Moderate atheroma	Marked arteriosclerosis, scars in heart muscle
8 XII 83	Strong man of 70	Slight atheroma	Mod arteriosclerosis
9 I-9	Emaciated man	Very marked atheroma, fusiform aneurysm	Marked arteriosclerosis
10 XIII-72	Emaciated man of 70	Marked atheroma	Mod arteriosclerosis
11 III 9	Emaciated old man	Moderate atheroma	Mod arteriosclerosis
12 IV 57	Emaciated man of 56	Moderate atheroma	Marked arteriosclerosis scars in heart-muscle
13 V-4	Strong man of 43	Little atheroma	Marked arteriosclerosis
14 IV-71	Strong man of 54	Slight atheroma	Marked arteriosclerosis, *gastric ulcer*
15 V-14	Strong man of 63	Moderate atheroma	Marked arteriosclerosis
16 VIII 45	Emaciated man of 65	Slight atheroma	Marked arteriosclerosis
17 IX-17	Strong man of 57	Slight atheroma	Marked arteriosclerosis
18 XII 28	Strong man of 50	Marked atheroma	Marked arteriosclerosis
19 XIV 33	Strong man of 56, painter	Slight atheroma	Slight arteriosclerosis except in kidneys

cases Figure 2 shows a section of one of the kidneys with moderate arteriosclerotic lesions, and Figures 3 and 4 specimens of "arteriosclerotic nephritis"

I shall discuss the results obtained under the following headings

1 Relation of arteriosclerosis to renal disease

2 Occurrence of hypertension and cardiac hypertrophy in arteriosclerosis and in "arteriosclerotic nephritis"

3 Relation of these conditions to lead-poisoning and gout

I RELATION OF ARTERIOSCLEROSIS TO RENAL DISEASE

Ever since the appearance of Gull and Sutton's[33] famous paper, in 1872, the relation of arterial disease to nephritis has been a very much-discussed topic Some of Gull and Sutton's histologic findings may be open to doubt, still I believe they deserve great credit for having first suggested that there is a disease in which the arterioles throughout the body are altered, which constitutes "a general morbid change of which contraction and atrophy of the kidneys is part and parcel" Their contentions have been disputed by many eminent authorities and just as vigorously embraced by others One could fill pages with literary quota-

33 Gull and Sutton The Pathology of the Morbid State Commonly Called Bright's Disease with Contracted Kidney (Arterio-Capillary Fibrosis), Medico Chir Tr , 1872, lv, 273

Heart	Condition of General Circulation	Other Important Lesions
Slight enlargement	Good	Carcinoma of stomach, cirrhosis
Slight general enlargement	Good	Carcinoma of esophagus, gouty deposits in kidneys and joints
Slight hypertrophy of left ventricle	Good	Chronic tuberculosis of lungs, gouty deposits in kidneys
Moderate hypertrophy of left ventricle	Marked chronic disturbance	
Moderate hypertrophy of left ventricle	Mod chronic disturbance	Gouty deposits in kidneys, embolism left middle cerebral artery
1¼ × normal, moderate hypertrophy and dilatation of both ventricles	Marked chronic disturbance	
1¼ × normal, moderate hypertrophy and slight dilatation of both ventricles	Marked chronic disturbance	
1¼ × normal, slight hypertrophy of left ventricle	Good	Cerebral hemorrhage, beginning carcinoma of prostate
Mod hypertrophy and dilatation of heart	Marked chronic disturbance	
Moderate hypertrophy of left ventricle	Good	Cerebral hemorrhage
Marked concentric hypertrophy of left ventricle	Good	Cerebral hemorrhage
Marked hypertrophy and slight dilatation of left ventricle	Recent disturbance in circulation	
Marked hypertr and slight dilat left ventricle, slight hypertr right ventricle	Good	Healed tuberculosis knee and right testis, chronic tuberculosis of right kidney, old and recent hemorrhage in brain
2 × normal, hypertrophy largely of left ventricle	Marked chronic disturbance	
2 × normal, hypertrophy and dilatation of entire heart	Marked chronic disturbance	
Marked concentric hypertr left ventricle	Slight chronic disturbance	Multiple areas of softening in brain
2 3 × normal	Marked chronic disturbance	
Very large, especially left side	Marked chronic disturbance	
3 × normal, very marked hypertrophy of left ventricle	Marked chronic disturbance	

tions for and against Comil and Brault,[21] for instance, in their excellent work are very much opposed to this view, Orth,[15] in his classic treatise on pathology, believes that in chronic interstitial nephritis the vascular changes are not essential and primary because their severity does not

TABLE 5.—ARTERIOSCLEROTIC NEPHRITIS ARRANGED ACCORDING TO SIZE OF HEART

The kidneys of the third series resemble very closely those in the second series, only the lesions are of a much more extreme degree. The capsule is noted adherent in all except one (V 18). The surface is granular, often full of large deep scars. The color of the kidneys is usually a dark purple with lighter gray or yellowish spots, in a few instances the kidneys, however, are described as diffusely pale (white contracted kidneys). The kidney tissue is very hard. The sizes vary from 15×5×3½ cm. (with some hypertrophy of the fatty tissue around the renal pelvis) to 8×4×3. On the cut surface the cortex is always found much reduced, to approximately 2-3 mm. in diameter. The markings of the cut surface are described as poor "or indistinct" in all cases. In several specimens the cortex was full of cysts of varying sizes. This was particularly noticeable in Cases XIII 86 and XII 13. The cases then, are typical examples of what is commonly described as advanced "granular atrophy" or as "the red contracted kidney" by the English authors.

Number		General Condition	Aorta	Peripheral Art
1	III-75	Stout old man	Marked atheroma	Marked arteriosclerosis
2	VIII 91	Emaciated woman of 41	Slight atheroma	Marked arteriosclerosis
3	VI 56	Emaciated man of 60	Normal	Slight arteriosclerosis
4	XIII 33	Emaciated young man, lead anemia	Atrophic	Mod. arteriosclerosis
5	XIII 42	Strong man of 50	Moderate atheroma	Marked arteriosclerosis
6	V 91	Moderately strong man of 69, painter	Normal	Little arteriosclerosis except in kidney
7	I 101	Fat old man	Marked atheroma	Little arteriosclerosis except in kidney
8	XII 32	Strong man of 65	Marked atheroma	Marked arteriosclerosis
9	III-10	Emaciated man of 62	Marked atheroma	Mod. arteriosclerosis
10	XIII 76	Emaciated man of 65	Moderate atheroma	Marked arteriosclerosis
11	I 16	Strong old man	Moderate atheroma	Mod. arteriosclerosis
12	I 109	Fairly strong man of 37	Slight atheroma	Marked arteriosclerosis, gastric ulcer
13	I-2	Strong man	Marked atheroma	Marked arteriosclerosis
14	VII 108	Strong old man, painter	Slight atheroma	Mod. arteriosclerosis
15	VIII 34	Emaciated man of 48, painter	Normal	Little arteriosclerosis except in kidneys
16	XIII 86	Strong man of 64	Moderate atheroma	Marked arteriosclerosis
17	VII-79	Emaciated man of 60	Considerable atheroma	Marked arteriosclerosis
18	VIII 55	Emaciated man of 77	Marked atheroma	Marked arteriosclerosis in kidneys
19	V-18	Stout man of 62	Slight atheroma	Marked arteriosclerosis
20	VII 99	Anemic man of 41	Normal	Little arteriosclerosis except in kidneys
21	XII 43	Emaciated woman of 42	Marked atheroma	Marked general arterio sclerosis
22	IX 57	Strong man of 65	Marked atheroma	Mod. arteriosclerosis except in kidneys
23	XIII-70	Anemic man of 70	Slight atheroma	Mod. arteriosclerosis
24	VII 59	Strong man of 49	Marked atheroma	Mod. arteriosclerosis scars in heart muscle
25	XIII 100	Emaciated man of 79, anemic	Marked atheroma	Marked arteriosclerosis, scars in heart-muscle
26	XIII-103	Anemic man of 31	Slight atheroma	Mod. arteriosclerosis

always correspond with the extent of the lesions, whereas Holsti,[34] Aufrecht,[30] and others are quite positive that in primary contracted kidneys the vascular lesions are general, that they precede the renal lesions and that many of the symptoms depend rather on them than on the associated disease of the kidneys Ziegler,[14] in his well-known article, says positively

Arteriosclerosis is one of the most frequent causes of contracted kidney Quite a proportion of small red kidneys are contracted as a consequence of arteriosclerosis The contraction of the kidney is only one manifestation of a disease of the vascular system extending over a large part of the body

(Die Arteriosklerose ist eine der haufigsten Ursachen der Nierenschrumpfung Ein nicht geringer Theil der kleinen rothen Nieren ist in Folge von Arterio

34 Holsti Ueber die Veranderungen der feineren Arterien bei granuloser Nierenatrophie, Deutsch Arch f klin Med, 1886, xxxviii, 122

Heart	Condition of General Circulation	Other Important Lesions
Brown atrophy	Good	Died after prostatectomy, gouty deposits in kidneys
Slightly enlarged	Good	Chronic tuberculosis of lungs
Slightly enlarged	Good	Lobar pneumonia, gouty deposits in kidneys
Slight hypertrophy of left ventricle	Slight recent disturbance	Gouty deposits in kidneys
Slight hypertrophy of left ventricle	Good	Acute anemia following operation
Slight hypertrophy of left ventricle	Good	Gouty deposits in kidneys and joints
Slight hypertrophy of left ventricle	Good	Suppurative pyelonephritis, gouty deposits in kidneys, joints skin, term sepsis
Large and firm	Good	Gouty deposits in kidneys
Moderate hypertrophy of left ventricle	Good	Carcinoma of esophagus
Moderate concentric hypertrophy of left ventricle	Good	Cerebral hemorrhage gouty deposits in kidneys
Moderate concentric hypertrophy of left ventricle	Good	Hemorrhagic diathesis
Marked concentric hypertrophy of left ventricle	Good	Acute pericarditis and peritonitis
Marked concentric hypertrophy of left ventricle	Marked chronic disturbance	Gangrenous ulcer on leg
Marked concentric hypertrophy of left dilatation of right ventricle	Good	Lead anemia, drop wrist, gouty deposits in kidneys and joints
1¼ × normal, concentric hypertr of left, hypertr and dilat of right ventricle	Good	Lead anemia drop wrist, gouty deposits in kidneys and joints, pericarditis
1¼ × normal, marked hypertr of left, some hypertr and dilat right ventricle	Good	Multiple hemorrhagic foci in brain
1½ × normal, marked concentric hypertr of left, slight hypertr right ventricle	Marked chronic disturbance	Chronic ulcer on back of left foot
1½ × normal	Good	Unresolved pneumonia, pericarditis
1½ × normal, hypertrophy and dilatation of both sides	Marked recent disturbance	
1½ × normal, concentric hypertr of left, mod hypertr and dilat of right heart	Marked subacute disturb	Gouty deposits in kidneys
1½ 2 × normal, marked concentric hypertrophy of left some hypertrophy and dilatation of right ventricle	Marked recent disturbance	
2 3 × normal, marked hypertr slight dilatation of left ventricle, hypertr and dilatation of right ventricle	Marked subacute disturb	Gouty deposits in kidneys, recent pleurisy
2 × normal, marked hypertrophy and dilatation of both sides	Marked chronic disturbance	Acute dysentery, gouty deposits in kidneys
3 4 × normal marked hypertrophy and moderate dilatation on both sides	Marked chronic disturbance	Gouty deposits in kidneys
Very large, hypertrophy and dilatation of both sides	Marked chronic disturbance	Chronic emphysema
Very large, marked hypertrophy of left, some dilatation of right side	Slight recent disturbance	Cerebral hemorrhage, gouty (?) deposits in kidneys

sklerose geschrumpft Die Nierenschrumpfung ist nur Theilerscheinung eines über einen grossen Theil des Körpers verbreiteten Erkrankung des Gefass-systems)

Still he insists that sometimes arteriosclerosis in kidneys is local and secondary Jores,[18] who in the last years has made a very careful study of arteriosclerosis and associated conditions, comes to this conclusion

The importance of the changes in the vessels for the destruction of the glomeruli, and thus for the development of contracted kidney, should be recognized in all forms of nephritis in which there is arteriosclerosis of the smallest vessels "

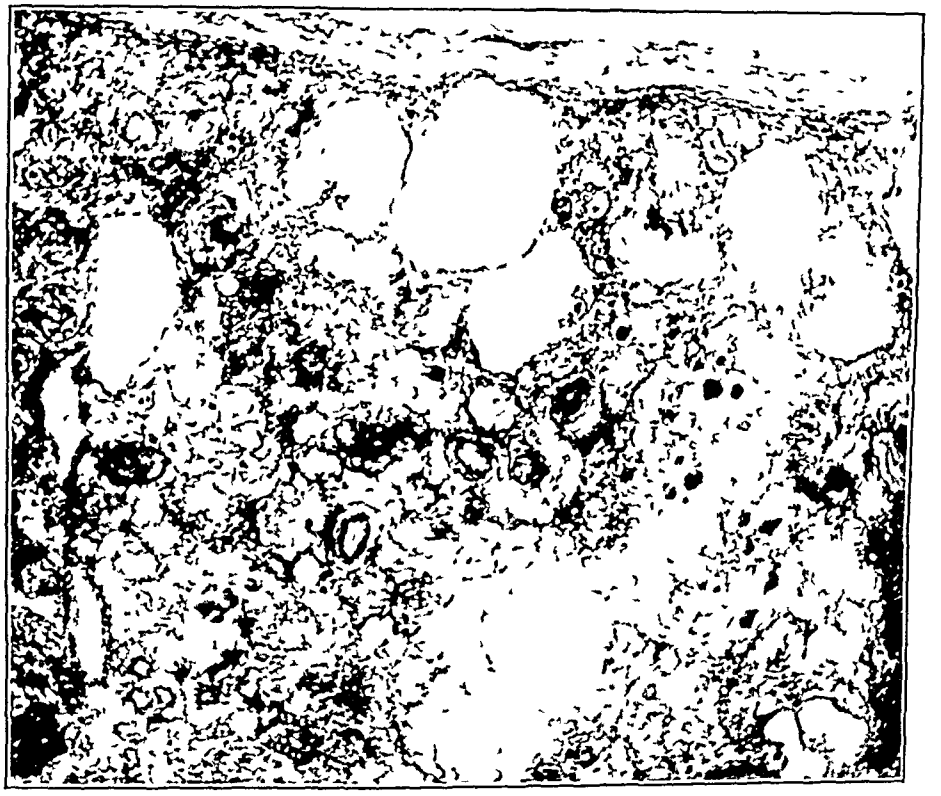

Fig 4 —50× VII 99 Marked arteriosclerotic nephritis Considerable cellular infiltration Many cysts Few hypertrophic remnants of normal tissue

I believe that a careful scrutiny of my cases cannot leave room for doubt in regard to the fact that the ordinary red granular contracted kidney is the result of general arteriosclerosis and that in many of these cases the general arteriosclerosis is much more important, in regard to the general condition of the patient, than the renal lesion which he may have at the same time Bradford,[36] from a similar point of view, elimi-

35 Die Bedeutung der Gefäss Alteration für das Zugrundegehen der Glomeruli und damit für die Entstehung einer Schrumpfniere ist für alle Formen von Nierenentzündung anzuerkennen, welche mit Arteriosklerose der kleinsten Gefässe einhergehen

36 Bradford Bright's Disease and its Varieties, Lancet, 1904, ii, 125

nates the red granular kidneys from Bright's disease altogether, which may seem a somewhat exaggerated position to hold but which certainly has something to commend it as it emphasizes that it is wrong to look at these conditions from the point of view of the kidney only, which is the common fault at present

The renal lesions, on the other hand, to my mind are not purely degenerative in character In the renal tissue, the inflammatory element in this general disease is much more evident than it is in the small arteries in which, as was first suggested by Friedemann,[37] and later very conclusively proved by Jores, the lesion consists largely in an apparently hyperplastic proliferation of the elastic tissue in the intima, whereas the inflammatory nature of the process is again much more marked in the large arteries, more especially in the aorta Roderer[38] of Philadelphia has quite recently very clearly expressed the same opinion from a clinical point of view He says

"Chronic interstitial nephritis is an inflammatory disease of the arteries possibly principally of the terminal arteries If this be correct then chronic interstitial nephritis is not the correct term to use to describe the disease Chronic arterial fibrosis would be a better term" "When the inflammation of the blood vessels in the kidneys extends to the parenchyma of the kidneys, then an examination of the urine will show casts and albumen" "Because the examination of the urine shows disease, it seems to me that is the reason why chronic interstitial nephritis has been called a disease of the kidneys"

II OCCURRENCE OF HYPERTENSION AND CARDIAC HYPERTROPHY IN ARTERIOSCLEROSIS AND ARTERIOSCLEROTIC NEPHRITIS

What are the facts in regard to the relation of vascular and renal disease to hypertension and cardiac hypertrophy?

In a little over one-third of our cases of marked general arteriosclerosis there is no cardiac hypertrophy These cases are very briefly abstracted below As shown there, this lack of evidence of hypertension may be due to general malnutrition in thirty-one cases, although, as Jores[39] has correctly pointed out, malnutrition is no bar to cardiac hypertrophy when caused by other conditions, there are also in addition six cases, or fifteen cases all told, in which the lack of cardiac hypertrophy might be referred to the more or less localized character of the arteriosclerotic lesions, it being a matter of common experience that rapidly developing aortic lesions, with aneurysms particularly, are not very apt

37 Friedemann Ueber die Veränderungen der kleinen Arterien bei Nierenerkrankungen, Virchows Arch f path Anat, 1905, clxxx, 543

38 Roderer Symptomatology and Diagnosis of Nephritis or Bright's Disease, Jour Am Med Assn, 1911, lvi, 1222

39 Jores Ueber die Beziehungen der Schrumpfniere zur Herzhypertrophie vom pathol anat Standpunkt, Deutsch Arch f klin Med, 1908, xciv, 1

to produce cardiac hypertrophy There remain twenty-one cases, or well over 10 per cent of all cases, in which no reason for the absence of cardiac hypertrophy seemed evident so far as I could see

ABSTRACT OF CASES OF MARKED ARTERIOSCLEROSIS WITHOUT CARDIAC HYPERTROPHY

A—CARDIAC HYPERTROPHY LACKING PROBABLY OWING TO GENERAL MALNUTRITION DUE TO

1 Malignant Tumor

1 I-18 marked atheroma of entire aorta, carcinoma of stomach

2 I-26 marked atheroma of aorta with fusiform aneurysm of arch carcinoma of stomach

3 I-50, marked atheroma of aorta, marked peripheral arteriosclerosis with scars in heart and in kidneys carcinoma of sigmoid flexure

4 III-24 marked atheroma of aorta and peripheral arteriosclerosis arterio sclerotic scars in kidneys carcinoma of esophagus

5 III-120, marked atheroma of aorta with dilatation, carcinoma of stomach

6 V 40 marked atheroma of aorta, arteriosclerotic scar in left kidney, carcinoma

7 VII-10 marked atheroma of aorta with multiple aneurysms carcinoma of esophagus

8 VIII-75 normal aorta marked peripheral arteriosclerosis carcinoma of stomach

9 IX 52 marked atheroma of aorta and peripheral arteriosclerosis, few arteriosclerotic scars in kidneys endothelioma of neck and cirrhosis

2 Senility

10 I 25 marked atheroma of aorta with aneurysm of thoracic aorta, old woman

11 I-77 marked atheroma of aorta and peripheral arteriosclerosis peptic ulcer senile atrophy of all organs

12 III-27, marked atheroma of aorta and peripheral arteriosclerosis, several small aneurysms in splenic artery and scars in myocardium extremely emaciated old woman

13 IV-7, marked atheroma of aorta emaciated man of 80

14 IV-88 localized atheroma of arch with aneurysm, emaciated man of 74

15 V-70, marked atheroma of aorta with fusiform aneurysm of arch, emaciated man of 62

16 VI-79 moderate atheroma of aorta, moderate arteriosclerosis of cerebral arteries old hemorrhages in brain, fairly strong woman of 71

17 VII-101 marked atheroma of aorta, aneurysm of arch large arterio sclerotic scars in kidneys beginning amyloid emaciated man of 69

18 VIII-60 localized atheroma of thoracic aorta with aneurysm, emaciated man of 66

19 IX-10, marked atheroma of aorta moderate peripheral arteriosclerosis, few small arteriosclerotic scars in kidneys, moderately well-nourished old woman

20 XIII-20 very marked atheroma of aorta, marked peripheral arterio sclerosis large arteriosclerotic scars in kidneys, extremely emaciated old man

3 Chronic Pulmonary Tuberculosis

21 III-79 marked atheroma of aorta with aneurysm of arch, chronic pulmonary tuberculosis

22 VIII-42 marked atheroma of thoracic aorta, large arteriosclerotic scars in kidneys chronic pulmonary tuberculosis, emaciated man of 58

23 XIII-8, slight atheroma of aorta, slight peripheral arteriosclerosis, large arteriosclerotic scars in kidneys, pulmonary tuberculosis

24 XIII-84, very marked atheroma of aorta, large arteriosclerotic scars in kidneys, chronic pulmonary tuberculosis, emaciation

4 Chronic Syphilis

25 XII-82, marked atheroma of thoracic aorta, marked arteriosclerosis of cerebral and renal arteries, few small arteriosclerotic scars in kidneys, syphilitic meningomyelitis, emaciated old man

5 Chronic Gastric Ulcer

26 VIII-10, no atheroma of aorta, marked peripheral arteriosclerosis, large arteriosclerotic scars in kidneys, peptic ulcer, emaciated man of middle age

6 Chronic Suppuration

27 I 93, marked atheroma of thoracic aorta with beginning formation of aneurysm, less of abdominal aorta, hematomyelia, emaciated from chronic suppurative cystitis and pyelitis

7 Addison's Disease

28 I-43, marked atheroma of aorta, Addison's disease

8 Unknown Cause, Probably Syphilis

29 III-54, local atheroma of descending aorta and aneurysm, emaciated negro of 41

30 VII-2 localized atheroma of thoracic aorta with moderate dilatation, emaciated man of 52

31 VII-106, localized atheroma of arch with aneurysm, emaciated man of 40

B —POSSIBLY ON ACCOUNT OF LOCALIZED CHARACTER OF LESIONS

32 VI-10, localized atheroma of arch with aneurysm, aorta otherwise normal, strong, well-nourished, syphilitic of 29

33 VI-125, marked atheroma of aorta, aneurysm of arch, strong old man

34 VI-126, marked atheroma of aorta, with dilatation of aorta, strong man of 58

35 VII-35, marked atheroma of entire aorta, stout man of 45

36 VII-72, marked localized atheroma of arch, sarcoma of brain, muscular well-nourished man of 42

37 VIII-69, localized atheroma of thoracic aorta with aneurysm, strong man, middle age

The limited extent of the lesions may also play a rôle in Cases I 18, 25, 26, 43, 93, III-54, 79, 120, IV-7, 88, V-70, VII-2, 10, 106, VIII-60 of Series A, in which the disease is more or less confined to the aorta, and in XIII-8 in which case the lesions are severe in kidneys only

C —UNEXPLAINED

38 III-1, marked atheroma of aorta with aneurysm of arch, few scars in left ventricle, strong, moderately well-nourished man of 50

39 III-80, marked atheroma of aorta with dilatation, moderate arteriosclerotic lesions in kidneys, old apoplectic cyst in brain, strong man of 60

40 V-126, marked atheroma of aorta, moderate peripheral arteriosclerosis, arteriosclerotic scars in kidneys, strong well-nourished man of 68

41 VI-77, marked atheroma of aorta, marked peripheral arteriosclerosis, arteriosclerotic scars in kidneys strong muscular man

42 VII 84, marked atheroma of entire aorta with beginning dilatation of arch, small arteriosclerotic scars in kidneys, strong old man

43 VII 92, localized atheroma of arch with aneurysm, many small arterio sclerotic scars in kidneys strong man of 49

44 VII 94 marked atheroma of aorta, marked general arteriosclerosis, many small arteriosclerotic scars in kidneys, diabetes, strong, stout man

45 VIII 29, marked atheroma especially of abdominal aorta, considerable peripheral arteriosclerosis involving coronary and cerebral arteries small arterio sclerotic scars in kidneys, fairly well nourished man of 70

46 VIII 30, marked atheroma of aorta, marked peripheral arteriosclerosis arteriosclerotic scars in kidneys strong man of 83

47 VIII 59, slight atheroma of aorta, marked arteriosclerosis of cerebral and of coronary arteries with softening of brain and scars in myocardium, strongly built, fairly well nourished old man

48 VIII 97, marked atheroma of aorta, slight arteriosclerotic lesions in kidneys, well nourished old man

49 IX 2, marked atheroma of aorta, aneurysm of left iliac artery marked arteriosclerosis of peripheral arteries, obstruction of coronaries, fairly well nourished man of 59

50 IX 12, localized atheroma of thoracic aorta, moderate arteriosclerosis of coronary arteries, large arteriosclerotic scars in left kidney, strong man of middle age

51 IX-38 marked atheroma of aorta with aneurysm, many small arterio sclerotic scars in kidneys, strong man of 66

52 IX 58, moderate atheroma of aorta, and marked peripheral arteriosclerosis, large arteriosclerotic scars in kidneys, cerebral softening, necroses in myocardium, gastric ulcer, muscular, well nourished man of 61

53 IX 60, moderate atheroma of aorta, with dilatation, marked peripheral arteriosclerosis with dilatation, few arteriosclerotic scars in kidneys, strong old man

54 XII 8, slight atheroma of aorta, large arteriosclerotic scars in kidneys, diabetes, strong, well nourished man of 60

55 XII-29, marked atheroma of aorta area of softening in brain, many small arteriosclerotic scars in kidneys, strong man of 59

56 XII-67, marked atheroma of aorta, marked general arteriosclerosis, arteriosclerotic scars and necroses in myocardium, few small arteriosclerotic scars in kidneys, strong man of 45

57 XIII 27, marked atheroma of aorta, aneurysm of abdominal aorta, moder ate peripheral arteriosclerosis, large arteriosclerotic scars in kidneys, strong man

58 XIV-3, very marked atheroma of aorta, aneurysm of abdominal aorta, few arteriosclerotic scars in kidneys, fairly well nourished man of 50

SUMMARY

Marked arteriosclerosis without cardiac hypertrophy in fifty eight cases, 35 per cent of all cases of marked arteriosclerosis

Lack of cardiac hypertrophy, possibly due to general malnutrition in thirty one cases

Malnutrition due to	Cases
Tumor	9
Senility	11
Chronic tuberculosis	4
Chronic syphilis	1
Chronic gastric ulcer	1
Chronic suppuration	1
Addison's disease	1
Unknown cause, probably syphilis	3
	31

Lack of cardiac hypertrophy possibly due to localized character of lesions in six cases, perhaps also in fifteen of those mentioned before
Lack of cardiac hypertrophy unexplained in twenty-one cases

If we look over the cases with cardiac hypertrophy in Tables 3, 4 and 5, we notice that, on the whole, the development of the cardiac lesion is associated much more closely with the degree of arteriosclerosis present than with the extent of the renal lesions

In the cases, for instance, represented in Table 3, the renal lesions are those which are so very commonly found at autopsy in otherwise healthy kidneys It seems highly improbable, therefore, that they were concerned in any way in the production of the general condition The cardiac hypertrophy in many of these cases is very well marked, just as much so as in cases with advanced renal lesions, and this has eventually led to the usual disturbances in the general circulation

There is well-marked evidence that the process in the heart begins with a concentric hypertrophy of the left ventricle, followed by insufficiency and dilatation, later involves the pulmonary circulation and the right ventricle and ends in general passive congestion and an entire breakdown of the circulatory mechanism In 1884, Lemcke[40] gave an excellent clinical and anatomical description of a very interesting case which evidently belongs to this first group

In Group 2 also (Table 4) the renal lesions are comparatively insignificant Here again we encounter the same condition of affairs

In Group 3 (Table 5) that of "arteriosclerotic nephritis," of which I wish to emphasize again that it is not separated by any sharp boundary from Group 2, there is one case without any cardiac hypertrophy, for the lack of which there is no explanation so far as I can see (see Case 1-III-75) The others show cardiac hypertrophy but in fully six of the twenty-six it is only slight, which in Cases 3 and 5 might be explained by the sudden early death of the individuals, still the fact remains that Patient 5 at least, in addition to the marked disease of the kidneys, had a well-developed general arteriosclerosis There are four more similar

40 Lemcke Beitrag zur Lehre von den ursachlichen Beziehungen zwischen chronischer interstitieller Nephritis und Endarteritis obliterans der kleinen Arterien des ganzen Korpers, Deutsch Arch f klin Med, 1884, xxxv, 148

cases, in which the hypertrophy of the left ventricle is only moderate, which leaves a well-marked cardiac hypertrophy in a little over half the cases only

Table 2, however, seems to suggest that the condition of the kidneys after all may be of some importance in the production of the cardiac hypertrophy because as is shown there, among the last 200 cases examined there were fourteen cases of marked general arteriosclerosis with small scars in the kidneys Only six of these showed cardiac hypertrophy There were also seven cases of marked general arteriosclerosis with large scars in the kidneys — cardiac hypertrophy in three whereas among eight cases of marked general arteriosclerosis with "arteriosclerotic nephritis," cardiac hypertrophy was present in all

If we now inquire whether we ever find cardiac hypertrophy without marked arteriosclerosis and without renal lesions not attributable to the usual other causes for such a condition we find among the 1 000 necropsies three cases which show this condition These cases are summarized below There is some arteriosclerosis in all of them but certainly not enough to account for the marked cardiac hypertrophy In the first case (I-107) the chronic bronchitis and emphysema which is present might explain changes on the right side of the heart but not at least according to my experience the general hypertrophy and dilatation of the entire heart In the second and third case there is not even that much of an explanation to be found, unless one wanted to look on Case 2 as a beer-drinker's heart which, to my idea, has a somewhat uncertain standing in pathology These cases are very similar to a case described by Jores[39] with slight peripheral arteriosclerosis, slight renal lesions and yet marked cardiac hypertrophy without apparently any adequate cause for the latter, except arterial hypertension of unknown origin It may be well to emphasize that these cases do not represent Huchard's "presclerosis, because the general symptom-complex of an old chronic condition with cardiac edema, thrombosis, embolism, etc is fully developed

SUMMARY OF CASES OF HYPERTROPHY OF THE LEFT SIDE OF THE HEART WITHOUT VALVULAR DISEASE AND WITHOUT MARKED ARTERIOSCLEROSIS

CASE 1 —I 107—C W, stout woman of middle age, heart very much enlarged, between two and three times size of fist, considerable hypertrophy and dilatation of both sides of heart very slight atheroma of aorta, marked arteriosclerosis in spleen, slight arteriosclerosis elsewhere, with few small arteriosclerotic scars in kidneys Barrel-shaped thorax, purulent bronchitis, emphysema of lungs General passive congestion, anasarca, ascites, hydrothorax, recent fibrinous pericarditis

CASE 2 —V 90 —P C, waiter, 68 years, marked hypertrophy and dilatation of both sides of the heart, very slight atheroma and slight dilatation of aorta, marked arteriosclerosis in spleen, no arteriosclerotic lesions in kidneys or elsewhere, slight emphysema, somewhat barrel shaped thorax, general cyanosis and edema, ascites, hydrothorax Brown induration of lungs Thrombi in peripro static veins, emboli in pulmonary artery, thrombosis in left ventricle, infarctions in kidneys

CASE 3.—V 54—W T F, strong old man, heart very large, nearly three times size of fist, hypertrophy more marked on left side, moderate arteriosclerosis of coronary arteries without obstruction, no arteriosclerotic lesions in kidneys or elsewhere, cerebral arteries normal, several old infarctions in kidneys, several areas of probably embolic softening in brain, cholelithiasis and chronic pancreatitis, old fibrinous pericarditis, death from lobar pneumonia

Jores also showed that hypertension in the arteries, such as sometimes exists in valvular disease, does not apparently lead to arteriosclerosis but to hypertrophy of the media of the small arteries Still, he does not seem to be ready to abandon his original conception, one which at present seems to have so many adherents (see Elliott[41] and Frank[42]), namely that

Fig 5.—150× VIII-70 Glomerulonephritis Acute stage Leukocytes and blood in glomerulus Beginning proliferation

the hypertension is the primary trouble which leads to both cardiac hypertrophy and general arteriosclerosis The latter would then appear largely as an excessive compensatory process followed by degeneration

It also seems quite evident from my cases that general arteriosclerosis cannot be the direct cause of the hypertension which produces the cardiac hypertrophy

41 Elliott Arterial Hypertension, Am Jour Med Sc 1910, cxxxix, 648

42 Frank Beziehungen zwischen Niere, Nebenniere und hohem Blutdruck in der menschlichen Pathologie, Berl klin Wchnschr, 1911, xlviii, 609

The theory of Hasenfeld,[43] that hypertension results only when the splanchnic area is affected by arteriosclerosis, is not borne out by my own observations

Actual observation then shows (1) that there may be marked general arteriosclerosis affecting the peripheral vessels without continued hypertension, (2) that the same is more rarely true when the arteriosclerosis is associated with extensive destruction of the kidneys, (3) that, at times, we have long-continued hypertension and cardiac hypertrophy, followed by cardiac insufficiency, of unknown origin, with little arteriosclerosis and slight renal lesions

This demonstrates to my mind, that (4) the interrelation between general arteriosclerosis arteriosclerotic renal disease, on the one hand and hypertension with resulting cardiac hypertrophy, on the other hand must be a rather loose one Jores[10] suggests that hypertension and arterial disease are coordinated phenomena or as he expresses it also

"Hypertrophy and arteriosclerosis appear to be forms of differently placed reactions of the vascular system to one and the same injury"[44]

I believe we must go much farther than this The evidence demands to my mind that we look on these conditions as frequently associated with one another but not directly connected Jores' assumption of a nova which at the same time affects the heart and the arteries, producing hypertrophy in the one and arteriosclerosis in the other does not suffice to cover the situation

The three cases summarized above seem to me to be a very serious argument against the proposition that hypertension in itself alone can be looked on as an adequate cause for general arteriosclerosis because in these cases there was evidently long-continued considerable hypertension and still there was very little arteriosclerosis Nor is an argument quite satisfactory which might be suggested by Senator's[45] paper in 1897 namely that the conditions are so frequently associated because their etiology is similar It is true, in his paper Senator speaks of the interrelation of arteriosclerosis and chronic nephritis only, pointing out that senility, gout, lead, alcohol, syphilis diabetes, tobacco, abnormal hereditary influences, seem to injure both arteries and kidneys simultaneously One might, however, wish to apply this idea to the more general question of the relation of hypertension to arteriosclerosis and arteriosclerotic renal disease as well, but the mere fact that the poisons suggested as active in these cases do not necessarily cause hypertension would speak against this idea

43 Hasenfeld Ueber Herzhypertrophie bei Arteriosklerose, etc Deutsch Arch f klin Med, 1897, lx, 215

44 Hypertrophie und Arteriosklerose erscheinen als verschieden lokalisierte Reaktionen des Gefasssystems auf dieselbe Schadigung

45 Senator Die Pathogenese der chronischen Nephritis, Berl klin Wchnschr, 1897, xxxiv, 820

From the evidence at hand we can only say General arteriosclerosis is a frequent disease probably of toxic origin (this would, to my mind, explain the evidences of inflammation in the larger arteries and in the kidneys) It is often the cause of a peculiar type of renal disease It is frequently but by no means regularly associated with hypertension and cardiac hypertrophy

III THE RELATION OF LEAD-POISONING AND GOUT TO GENERAL ARTERIOSCLEROSIS AND ARTERIOSCLEROTIC NEPHRITIS

I have had occasion to point out before that lead is the only definite etiological factor known in this type of renal lesion Attempts have been

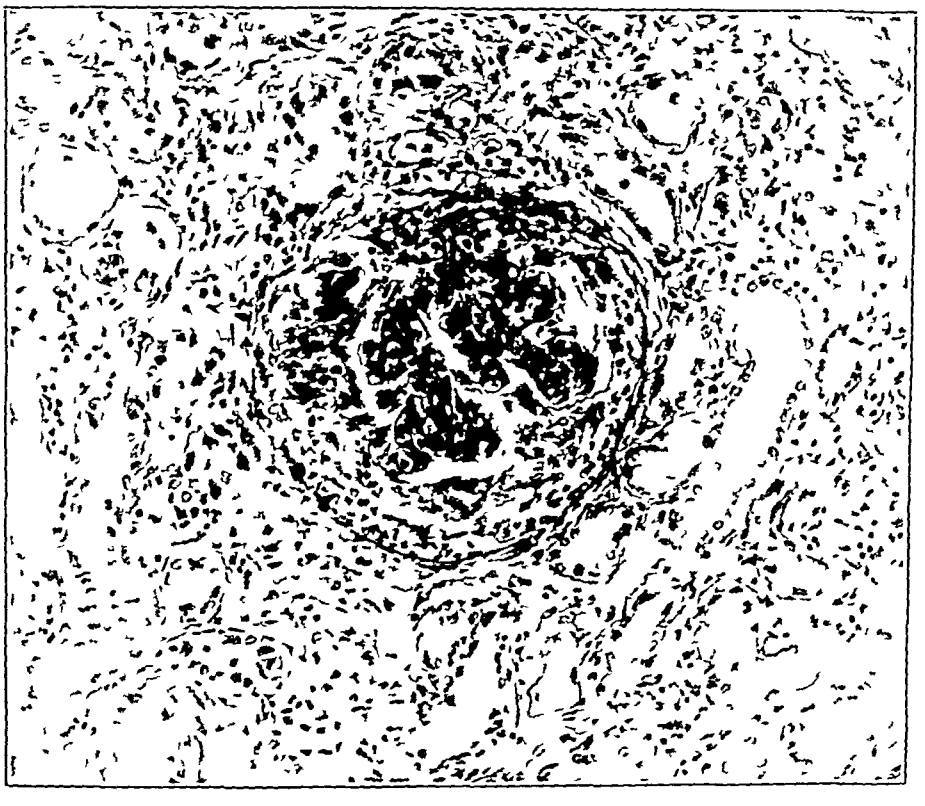

Fig 6—150x VIII-70 Glomerulonephritis Later stage

made to separate out the lead kidneys from the ordinary arteriosclerotic kidneys, but, I believe with little success In my specimens at least, I fail to find anything which would suggest any well marked difference

The important rôle played by lead-poisoning in the production of these conditions is very clearly brought out by our tables and it is particularly suggestive that among the severest cases in Table 5 the cases of lead-poisoning are especially numerous and well marked

Below are given some data in regard to the interrelation of gout, on the one hand and general arteriosclerosis and "arteriosclerotic nephritis," on the other The frequent association of the two conditions is well known and hardly needs any additional confirmation I may say that I have been interested in this relation for many years, even before these

cases were collected I am fairly positive, therefore, that gouty lesions were not overlooked in many instances, because they were carefully searched for

Summary of Relation of Lead Poisoning and of Gout to Arteriosclerosis and Arteriosclerotic Nephritis

Among the 1,000 cases examined lesions suggestive of gout were discovered in thirty instances In twenty-three of these cases uric acid deposits were found in the kidneys only in seven cases both in kidneys and in joints

In eight of these thirty cases the kidneys showed slight arteriosclerotic lesions only, curiously in all of these cases the deposits were limited to the kidneys In three of the eight cases with slight renal lesions the hearts and blood vessels were fairly normal in the remaining five there was a marked general

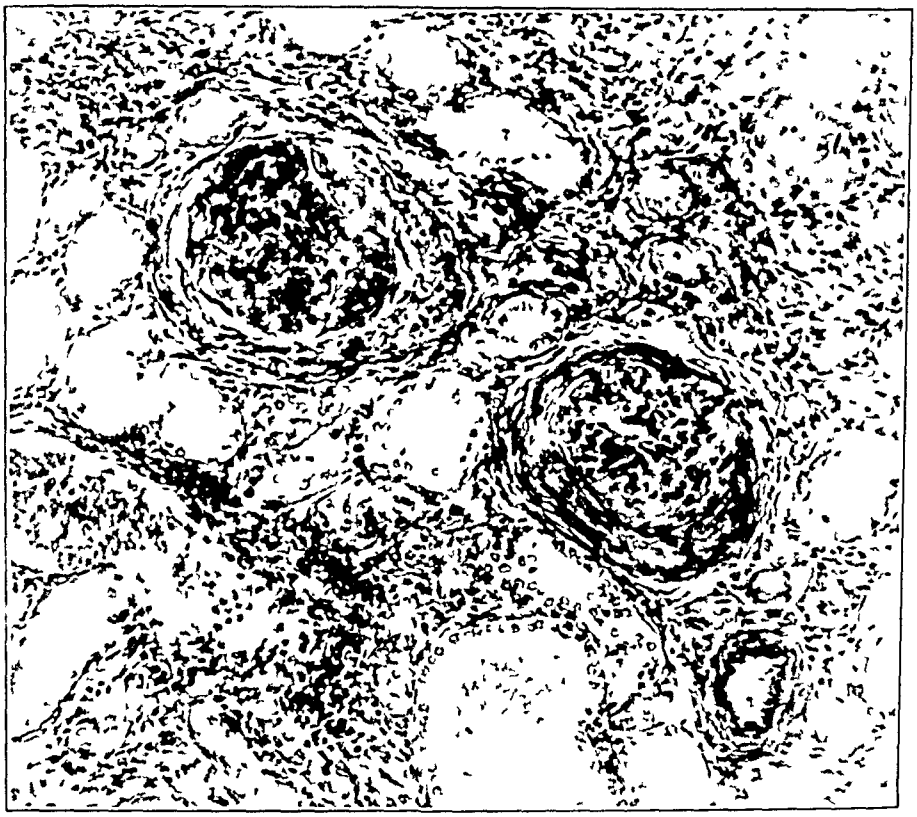

Fig 7—150× V 147 Glomerulonephritis Still later stage Beginning interstitial lesions

arteriosclerosis and cardiac hypertrophy There were ten cases with large arteriosclerotic scars in the kidneys, in seven of these the deposits were confined to the kidneys, in three they were present in both joints and kidneys In six of these ten cases the hearts and blood vessels were fairly normal, whereas in four the arteriosclerosis was general and associated with cardiac hypertrophy In twelve of the thirty gouty cases there was arteriosclerotic nephritis, which is nearly 50 per cent of all cases of arteriosclerotic nephritis which were observed in the entire series of 1,000 cases In these twelve cases, the deposits were found in the kidneys only eight times, in joints and kidneys four times In all these cases the arteriosclerotic process was general and well marked with cardiac hypertrophy in all except one

Among these thirty cases of gout, three were undoubted cases of lead-poisoning and in twelve others this was highly probable Altogether then there were fifteen or just 50 per cent of them which were probably due to lead

There were three cases in which the occupation suggested chronic lead-poisoning, in which there was general arteriosclerosis, some renal lesions and cardiac hypertrophy without gouty manifestations

The findings in my cases seem to suggest that in gout quite generally the first deposits occur in the kidneys, also that the renal lesions associated with gout are practically always of the arteriosclerotic type There is one apparent exception in our series, in Case 10 of the cases of acute and subacute glomerulonephritis (Table 6) gouty deposits were found in the pyramids In this case, however, there is also present in the kidneys considerable arteriosclerosis with many arteriosclerotic scars To a certain extent our observations support Muller's[24] statement that in lead-gout the lesions are apt to be much more serious than in gout due to other causes

Fifty per cent of our cases of gout were probably lead-gout — which, taking into account the rather imperfect histories which accompanied them, is a remarkably high percentage Our cases also show clearly that chronic lead-poisoning in man eventually is practically always accompanied by gouty diathesis, only three exceptions were noted to this rule

It is interesting to note that in 50 per cent of all cases of "arteriosclerotic nephritis," gouty deposits were observed in the kidneys or in both joints and kidneys Could gout be the result of the renal lesions, as has been suggested by some of the French authors? Hardly, when one takes into consideration those cases in which the renal lesions are so very slight

As we know so very little about the true nature of the gouty diathesis, it seems premature to discuss its exact relation to the arterial and renal changes I hardly think that it is safe to assume, from the evidence presented, that gout should be looked on as an etiological factor in the production of arteriosclerosis and arteriosclerotic renal lesions, although I myself was very much inclined to this view at one time There are many other relations possible besides those of direct cause and effect between two phenomena which are frequently associated, the truth of which statement is not always sufficiently borne in mind in investigations of this character

There remain to be considered forty-five cases of what Bradford[36] would consider true Bright's disease, of these, seventeen are cases of acute and subacute glomerulonephritis, all of a hemorrhagic character, seventeen others are large white kidneys all associated with amyloid, and eleven are secondary contracted kidneys in which we find a constant association of chronic glomerulonephritis with hemorrhages and a usually local deposit of a material which closely resembles, if it is not identical with, amyloid

Number and Age	Probable Cause	Heart	Blood Vessels
1 III 8 23 yrs	Chronic septic endocarditis	Hypertrophy due to valvular disease	Normal
2 II-1 Middle age	Chronic pulmonary tuberculosis, streptococcus sepsis	Brown atrophy	Slight atheroma of aorta
3 VIII 81 Middle age	Subacute septic endocarditis	Hypertrophy due to valvular disease	Normal
4 VII 32 Middle age	Pneumococcus sepsis following compound fracture of tibia	Normal	Normal
5 VIII 19 10 yrs	Subacute septic endocarditis	Hypertrophy due to valvular disease	Normal
6 XIII 64 10 yrs	Subacute septic endocarditis	Hypertrophy due to valvular disease	Normal
7 VIII 9 56 yrs	Chronic septic endocarditis	Hypertrophy due to valvular disease	Marked atheroma of aorta
8 XIII-108 15 yrs	Chronic septic endocarditis	Hypertrophy due to valvular disease	Moderate atheroma of aorta
9 VII 62 33 yrs	Chronic septic endocarditis	Hypertrophy due to valvular disease	Normal
10 VII 51 30 yrs	Poisoning with white precipitate of mercury 1½ months before death	¾ normal size	Slight atheroma of aorta
11 XII 35 40 yrs	Subacute septic endocarditis	Hypertrophy due to valvular disease	Normal
12 XII 3 50 yrs	Chronic sepsis from abscess on toe	Slightly hypertrophic on left side	Slight atheroma of aorta
13 XII 69 10 yrs	Chronic sepsis scabies and furunculosis	Slight hypertrophy of left ventricle	Moderate atheroma of aorta
14 I-110 Old man	Chronic sepsis, bronchopneumonia with cavitation	Slight hypertrophy and dilatation of heart	Slight atheroma of aorta
15 V 147 32 yrs	Chronic sepsis from leg ulcers	1½ normal, marked hypertrophy of left ventricle	Normal
16 VIII 70 65 yrs	Chronic syphilis, sepsis suspected but not proved	Atrophic	Marked atheroma of aorta and peripheral arteriosclerosis
17 VIII 76 61 yrs	Cirrhosis with hemorrhagic diathesis, sepsis suspected but not proved	Brown atrophy	Slight atheroma of aorta

Kidneys Gross Appearance	Kidneys Microscopical Lesions
Cortex swollen, opaque, some infarctions	Septic embolus, anemic necrotic infarct, no arteriosclerosis, leukocytosis in hyperemic glomeruli, in some, necrosis of few loops and beginning glomerulonephritis, blood in many tubules, few small foci near glomeruli show diffuse infiltration with polymorphonuclear leukocytes and beginning proliferation of connective tissue
13½ × 5½ × 4½ cm, dark reddish brown, full of small hemorrhages, cortex opaque edematous	No arteriosclerosis, glomeruli anemic, swollen, very cellular, capsular spaces wide, no desquamation of epithelium, much hemorrhage in tubules, pigmented casts
13 × 8 × 3½ cm, no gross lesions noticed	Slight arteriosclerosis, few arteriosclerotic scars, glomeruli large, hyperemic, cellular, partly infiltrated with leukocytes, swelling of capsular epithelium, much blood in tubules, many blood-casts, necrosis of epithelium, near glomeruli small areas of cellular infiltration and beginning formation of connective tissue
16 × 7½ × 5 cm edematous, opaque, full of hemorrhages	Few small arteriosclerotic scars, glomeruli large, very cellular, capsular spaces dilated, filled with granular material, leukocytes and red blood corpuscles, beginning formation of fibrin, hemorrhages in many tubules
12½ × 6½ × 3½, brown, many hemorrhages, cortex wide, opaque	Few small arteriosclerotic scars, glomeruli cellular, fusiform cells between loops and in capsular spaces, formation of fibrous tissue in some, many small foci of cellular infiltration, fatty degeneration of epithelium, hemorrhages and pigmented casts
12½ × 6½ × 4 capsule adherent, surface granular, cortex grayish-red, wide, opaque	No arteriosclerosis, glomeruli large, very cellular, beginning formation of fibrous tissue between vascular loops in many, blood and polymorphonuclear leukocytes in capsular spaces and in some tubules, few areas of cellular infiltration and beginning proliferation
Large, hyperemic, many small hemorrhages	Moderate arteriosclerosis, few small arteriosclerotic scars, in some glomeruli necrosis of loops, formation of hyaline fibrin, organization from pedicle or from wall, finally fibrosis, cellular infiltration and new formation of connective tissue around glomeruli, much degeneration and necrosis in tubules, many hemorrhages, pigmented casts
12½ × 7 × 4 cm, pink on white background, edematous, cortex pale, deep scar at lower pole of right kidney	Little arteriosclerosis, marked subacute and chronic glomerulonephritis much granular and fatty degeneration of epithelium, few casts few hemorrhages, glomeruli infiltrated with polymorphonuclear leukocytes, marked diffuse new formation of cellular connective tisue
14 × 4 × 5½ cm, cortex wide, pale, moist, opaque, putty like, surface mottled, gray and red	No arteriosclerosis, blood and hyaline fibrin between vascular loops and in capsules of glomeruli, marked subacute glomerulonephritis, marked granular degeneration, hemorrhages in tubules, many casts, marked new formation of cellular connective tissue with beginning shrinkage
12 × 5½ × 3½ cm, capsule adherent, surface granular, markings obliterated, many uric acid infarcts in pyramids	Many arteriosclerotic scars of moderate size, subacute glomerulonephritis with adhesions to capsules and marked, papillary proliferation of capsular epithelium necrosis and degeneration of tubular epithelium, blood and leukocytes in vessels, slight diffuse new growth of cellular connective tissue
Large, hyperemic	Moderate arteriosclerosis, in glomeruli, hemorrhages, fibrinous deposits, subacute and chronic glomerulonephritis, marked granular degeneration of epithelium, many casts, blood in tubules, large areas of new-formed connective tissue around glomeruli
Swollen, cortex light grayish brown, pyramids dark brown, small hemorrhages	Slight arteriosclerosis, in glomeruli, much blood and fibrin, some necroses, subacute glomerulonephritis, much blood in tubules, necrosis and desquamation of epithelium in many tubules, few casts, marked diffuse new formation of cellular connective tissue with much leukocytic infiltration
Left normal size, right distinctly shrunken, surface rough, cortex pale, thin	Moderate arteriosclerosis, marked subacute glomerulonephritis, few hemorrhages, few leukocytes in tubules, granular and fatty degeneration of epithelium, few casts, much cellular infiltration and much diffuse new formation of cellular connective tissue
14½ × 7 × 4 cm, pale reddish gray, with lighter dots, cortex wide, opaque, many small hemorrhages	No arteriosclerosis, marked subacute glomerulonephritis, marked granular and fatty degeneration of epithelium, blood and pigment in tubules, moderate irregular cellular thickening of interstitial tissue with pigmentation
12×5½×4, capsule adherent, surface uneven, cortex nearly white, opaque	Moderate arteriosclerosis, marked subacute and chronic glomerulonephritis, some fatty degeneration of epithelium, few casts, much blood and leukocytes in tubules, marked cellular infiltration and new formation of connective tissue with beginning shrinkage
Marked hyperemia and edema	Marked arteriosclerosis, in glomeruli, blood and fibrin, subacute and chronic glomerulonephritis, fatty degeneration of epithelium, many casts, much blood and leukocytes in tubules, very marked diffuse cellular infiltration and new formation of fibrous tissue with beginning shrinkage in places
10 × 6 × 2½, surface coarsely granular, tissue hyperemic soft, edematous, cortex narrow	Marked arteriosclerosis, slight subacute glomerulonephritis, capsular spaces free, fatty degeneration and necrosis of epithelium, much blood in tubules and pigmentation of epithelium, very marked, diffuse, somewhat irregular cellular infiltration and new formation of cellular fibrous tissue, atrophy of many tubules

ACUTE AND SUBACUTE GLOMERULONEPHRITIS

The seventeen cases representing this group are contained in Table 6 Several of them were encountered in comparatively young individuals Practically all of them were suffering from a chronic septic process, most frequently from subacute or chronic septic endocarditis due to diplostreptococci The condition is very similar in Case 2 in which we have a streptococcus sepsis following chronic pulmonary tuberculosis, in Case 4 with a pneumococcus sepsis following fracture, in Case 15 with a chronic sepsis following leg ulcer In Case 10 there were large ulcers in the intestines which were possibly the portal of entry of a septic infection, because so far as I know, mercurial poisoning in itself does not produce glomerulonephritis In Case 12 the infection started from an abscess on one of the toes, in Case 13 there was scabies and general furunculosis in Case 14 the septic process seems to have commenced in the lungs In Cases 16 and 17 only the existence of a septic process is not definitely established but the numerous polymorphonuclear leukocytes in the renal lesions at least in Case 16 make the existence of a septic process fairly probable

The intimate relation of glomerulonephritis to chronic sepsis is also shown by the following figures Among the 1 000 cases investigated there were seventy-three cases of endocarditis of these ten were cases of recent and twenty-seven cases of healed endocarditis No glomerulonephritis was found in these thirty-seven cases Among the remaining thirty-six cases of subacute and chronic septic endocarditis there were fourteen cases of glomerulonephritis

Among the 1,000 cases there were also twenty-eight cases of general sepsis without endocarditis Of these twenty-one were acute and without glomerulonephritis, seven chronic with glomerulonephritis in six

The relation of sepsis to subacute and chronic nephritis has received some mention in literature but its true extent has hardly been sufficiently appreciated As early as 1884, Ernst[46] reports two cases of acute nephritis and one case of chronic parenchymatous nephritis with bacterial findings In 1877, Baitels[11] mentions as etiological factors persistent suppuration, inveterate syphilis phthisis and possibly malaria Blum,[47] in 1890, states that chronic nephritis is caused by infectious diseases perhaps more frequently than is commonly believed, and reports a case, confirmed by autopsy, which followed parotitis epidemica Councilman,[17] in 1897, found fifteen cases of sepsis in fifty-two cases of acute and subacute glomerulonephritis Nicholls,[48] in 1899, believes that infection is

46 Ernst Zur Aetiologie der Nephritis, Zurich, 1884

47 Blum Ueber die Aetiologie der Nephritis, Deutsch Arch f klin Med, 1890, xlvii, 193

48 Nicholls Contributions to the Study of Bright's Disease, Montreal Med Jour, 1899, xxviii, 161

important in all cases of chronic nephritis, having demonstrated to his satisfaction the presence of minute diplococci and sometimes of bacilli in the tissues and in the urine in many cases Thompson[49] also points out the frequency with which chronic nephritis follows sepsis In 1910, Curschmann[50] makes the very definite statement that sepsis is frequently the cause of acute and subacute nephritis of hemorrhagic type which according to him unfortunately frequently becomes chronic He believes that it is usually toxic in origin but sometimes due to actual infection of the kidneys, when streptococci may appear in the urine He also

Fig 8—90x II-4 Parenchymatous nephritis and amyloid Large white kidney Beginning glomerulonephritis beginning interstitial lesions

speaks of the relation of tonsillitis to these septic processes followed by nephritis, a matter which has also been discussed by other observers

The most characteristic feature in the gross appearance of these kidneys with acute and subacute glomerulonephritis is the very marked diffuse hyperemia of the cortex, which is frequently associated with the occurrence of numerous plainly visible petechial hemorrhages Often

49 Thompson Unsuspected Nephritis in Septic Infections Brit Med Jour, 1907, ii 737

50 Curschmann Beziehungen entzundlicher Mandelaffektionen zu Infektionskr, Munchen med Wchnschr, 1910 lvii 284

there is also considerable edema with swelling and the tissues are soft, putty-like When there is much formation of pigment, the color of the kidneys may be distinctly brown, which was especially well marked in our Case 12 The surface of these kidneys is usually smooth but this may be somewhat modified by the pressure of arteriosclerosis and the development of arteriosclerotic scars

Histologically, the glomerular lesions naturally attract most attention There is hardly any other condition in the kidneys, or elsewhere for that matter, which has received as much careful study as the histology of glomerulonephritis, ever since it was first discovered by Klebs and described in his "Handbook of Pathological Anatomy" Goermans[51] (1869) Langhans (1879,[52] 1883,[53] 1888[54]), Cornil and Brault (1885),[55] Obrzut[55] (1888), Ribbert[56] (1888), Boehm[57] (1897) Councilman[16] (1897) Cornil[58] (1900) Engel[59] (1901), Tschistowitsch[27] (1903), Herringham and Thursfield[60] (1904) and last but not least Lohlein[18] (1907) have published important contributions to this subject and still there remains considerable uncertainty in regard to some of the finer histological detail My impression is that in many cases at least, there is first a hemorrhagic exudate poured into the capsular space of the glomeruli as shown in Figure 5 which coagulates and is later organized (see Figures 5, 6 and 7) a view strongly advocated by Cornil and by Engel Eventually the process terminates in a more or less complete fibrosis of the affected glomeruli which is similar to that which occurs in arteriosclerosis but, to my mind, still sufficiently distinct to be differentiated from it which differentiation is facilitated by the usual finding of the earlier unmistakable stages of the process even in very chronic cases of glomerulonephritis Associated with this there are some interesting capsular changes which we need not dwell on here I do not quite

51 Goermans La Capsule de Bowman dans les infl chroniques des reins, Rec des travaux anat path du lab Boerhave, 1869

52 Langhans Ueber die Veranderungen der Glomeruli bei der Nephritis, Virchows Arch f path Anat, 1879, lxxvi, 85

53 Langhans Ueber die entzundlichen Veranderungen der Glomeruli, etc, Virchows Arch f path Anat, 1883, xcv, 193

54 Langhans Ueber die entzundlichen Veranderungen der Glomeruli, Virchows Arch f path Anat, 1888, cxii, 1

55 Obrzut Nouvelles recherches sur la pathogénie de la glomérulonephrite, Rev de méd, 1888, viii, 689

56 Ribbert Beitrag zur path Anatomie der Glomeruli, Fortschr d Med, 1888, vi, 490

57 Boehm Beitrag zur path Anatomie der Malp Korperchen der Niere, Virchows Arch f path Anat, 1897, cl, 52

58 Cornil La glomérulité, Presse méd, 1900, xviii, 1, 177

59 Engel Glomerulitis adhæsiva, Virchows Arch f path Anat, 1901, clxiii, 209

60 Herringham and Thursfield The Glomerular Lesions of Diffuse Nephritis, Tr Path Soc, London, 1904 lv, 283

understand why Lohlein[61] in his last article on the subject wishes to separate those forms which occur in septic endocarditis from what he terms true glomerulonephritis If he had fully recognized the importance of sepsis in the production of the lesions in all cases, I do not believe that he would have favored such an opinion

The presence of many polymorphonuclear leukocytes in the blood-vessels and in the hemorrhagic exudate is very characteristic and well shown in Figures 5 and 6 Blood-casts and pigmented hyaline casts are naturally frequent The epithelium usually shows well-marked degenerative changes, often ending in necrosis In practically all cases there is

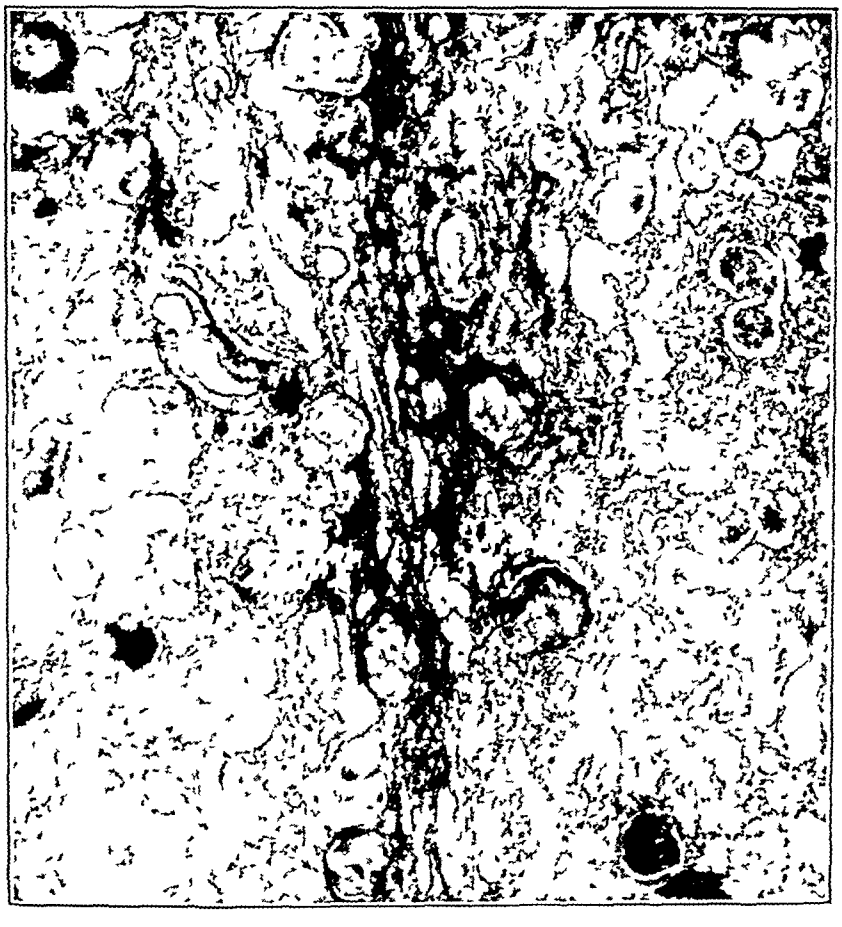

Fig 9—50× VIII-94 Parenchymatous nephritis and amyloid Large white kidney Advanced glomerulonephritis and advanced interstitial lesions

some cellular infiltration, at least in the vicinity of the diseased glomeruli, and eventually there may be quite a considerable, more or less diffuse proliferation of the interstitial tissue with formation of fibrous tissue and shrinkage The inflammatory changes in the glomeruli and those in the interstitial tissue seem to be widely independent from one another This is most clearly illustrated by Case 17 (VIII-76), in which there is remarkably little change in the glomeruli and a very well-marked diffuse overgrowth of the connective tissue

61 Lohlein Pathol Anatomie der hæmatogenen Nephritis Ergebn d allg Path u path Anat (Lubarsch and Ostertag) 1910 xiv, ii, 874

There is also no constant relation between the extent of the disease in the glomeruli and the amount of epithelial degeneration which one should expect, according to Lohlein's theory that the epithelial changes depend on circulatory difficulties resulting from the disease of the glomeruli. I feel constrained to assume that the epithelial lesions are toxic in origin and I cannot feel that there is as little foundation for such an assumption as Lohlein wishes us to understand.

It does not coincide very well with Loeb's[62] idea, that there is a particularly close relation between glomerular disease and hypertension followed by cardiac hypertrophy, when we notice that in those cases in which other reasons for cardiac hypertrophy are absent the hearts are uniformly small. In Cases 12, 13, 14 and 15 only is there a slight hypertrophy which however as there is evidently no other factor to explain it must be definitely ascribed to the condition of the kidneys.

LARGE WHITE KIDNEYS WITH AMYLOID DEGENERATION

After what has been laid down in literature on the subject it is certainly quite surprising to find that not only all large white kidneys in our series are associated with amyloid but also that in all cases of amyloid degeneration, in which the condition was well advanced, there was a large white kidney associated with it.

Among the 1 000 necropsies there were thirty-seven cases of amyloid degeneration, nine of these showed incipient lesions either in the spleen only (six cases), in spleen and liver only (one case) or just beginning amyloid of the kidneys (two cases). The rest showed associated parenchymatous nephritis. In three of these, the lesions were in the incipient stage, in the others there are well-developed large white kidneys. The close relation between amyloid degeneration and large white kidneys has, of course, been known to all observers, but a differentiation between amyloid kidneys and chronic parenchymatous nephritis has been attempted again and again, most frequently "for clinical reasons."

Apart from this, my series adds only little to what is already well known. The gross appearance of these kidneys has been described too often to need further comment.

The incipient glomerular lesions are well shown in Figure 8, which also brings out one important point, namely, that from the beginning there is considerable, often quite diffuse cellular infiltration of the interstitial tissue which seems to commence in the vicinity of the glomeruli. In the beginning there is sometimes a very marked infiltration of the tissues with polymorphonuclear leukocytes. The presence of leukocytes and, especially in the later stages, of blood in the tubules connects these cases

62. Loeb: Blutdruck und Herzhypertrophie bei Nephritikern, Deutsch. Arch. f. klin. Med., 1905, lxxxv, 348.

with my series of acute and subacute glomerulonephritis, which connection appears particularly close when we notice that almost from the beginning the amyloid degeneration of the glomeruli is associated with signs of glomerulonephritis, which after a while become more evident and eventually leads to fibrosis as shown in Figure 9 At this time, the chronic interstitial changes are well marked and evidences of shrinkage make their appearance The epithelial lesions are well marked in all cases and show practically in all instances the peculiar coarsely granular degeneration in which doubly refracting lipoidal granules or droplets

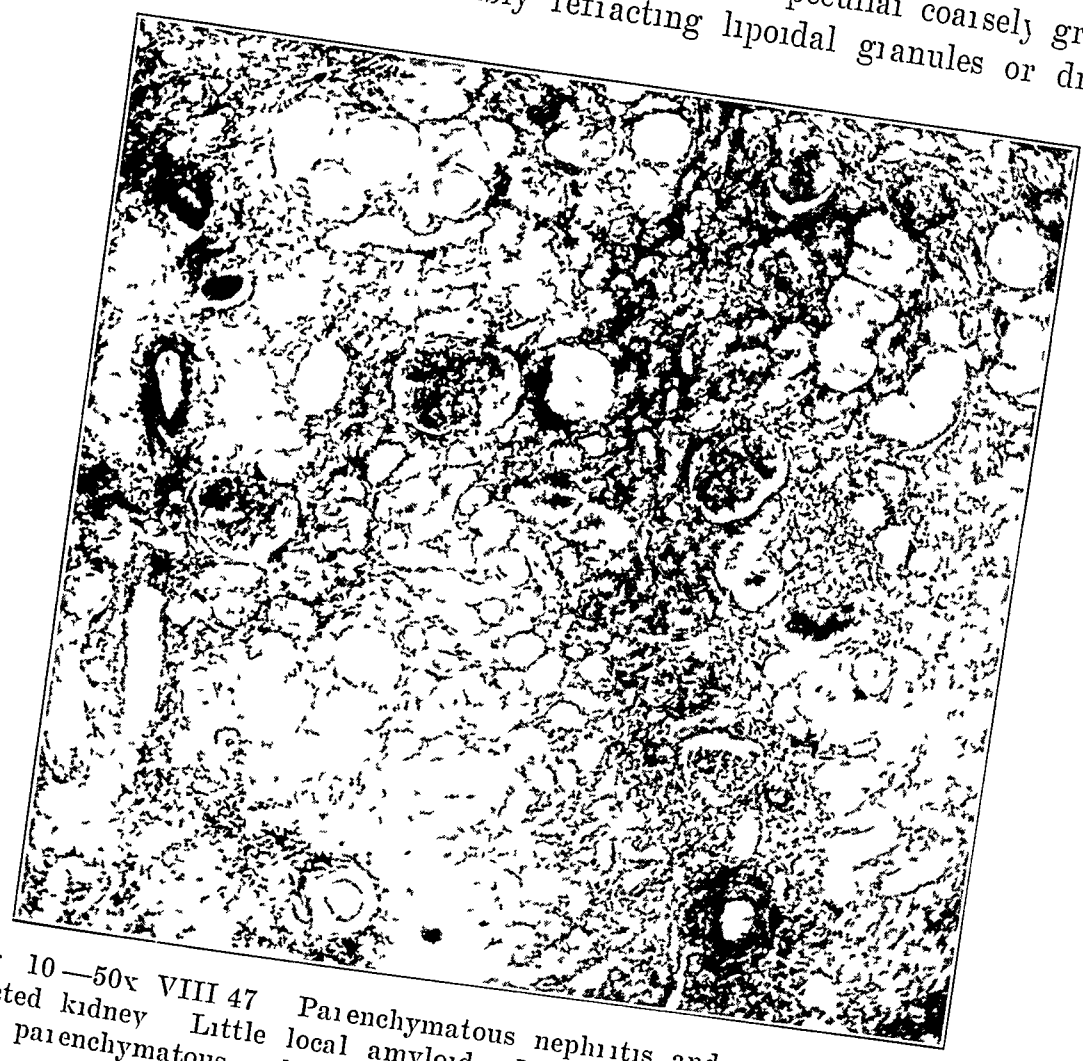

Fig 10—50x VIII 47 Parenchymatous nephritis and amyloid Secondary contracted kidney Little local amyloid Moderate glomerulonephritis Very marked parenchymatous and interstitial lesions Obscure sepsis

make their appearance in the protoplasm, a condition which has quite a literature of its own

The presence of an immense number of casts is also quite characteristic of this type of renal lesion

Etiologically also the two groups have much in common The relation of chronic sepsis to amyloid degeneration is too well understood to need any mention In chronic pulmonary tuberculosis, which is the most common cause of these large white kidneys, we have a typically septic condition with well marked general intoxication Syphilis can be easily

looked on as a peculiar type of general sepsis This disease may also cause some predisposition to cryptogenic septic infections It is interesting to note the comparatively large number of cases of cirrhosis associated with large white kidneys (Cases 9 10 13, also Case 19 of the next group), which, to my mind throws an interesting sidelight on this disease which still appears so very obscure from many points of view

The blood-vessels are normal or show accidental lesions it is also a well-known fact that in these cases the heart is usually small, sometimes normal and very rarely enlarged In my series, the latter is the case in one instance only (Case 9) It is possible that there was sufficient general arteriosclerosis present in this instance to account for this apparent exception

SECONDARY CONTRACTED KIDNEYS

It is to a great extent due to Lohlein's[19] work that the comparative frequency of secondary contracted kidneys has been definitely proved The older authorities, in Germany at least (like Bartels), look on them as great rarities Occasional cases were reported by Dickinson,[9] Leyden,[23] Aufrecht,[63, 59] Held[64] and Eisenlohr[65] Cornil[21] surmised that many cases of old contracted kidney might have had a more acute inflammatory origin, but did not prove his point by any direct observation From the clinical and pathological material in Leipsic Lohlein[19] succeeded in collecting quite a number of cases which clinically as well as anatomically were evidently examples of secondary contracted kidneys He found in all of them changes in the glomeruli referable to former glomerulonephritis and points out that, on account of the comparative ease with which he discovered such cases, they cannot be so rare as was formerly believed

My observations bear this out in every respect, except that in addition to the ordinary glomerulonephritis there is present usually in the glomeruli a peculiar hyaline substance which in some cases I am sure is amyloid In others it was not discovered until after the specimens had been hardened and the possibility of obtaining a typical reaction was more or less interfered with by the hardening process When tested with methyl violet, the reaction in these cases was at least as strong as in other specimens with known amyloid It will remain for the future to decide whether the substance is real amyloid in all cases It is certainly closely related to it It stains, for instance, exactly like amyloid with the van Gieson method The occurrence of this peculiar "hyaline" in chronic

63 Aufrecht Eine 20 Jahre dauernde Nephritis, etc, Deutsch Arch f klin Med, 1888, xlii, 517

64 Held Zur Kenntnis der glatten weissen Schrumpfniere, Beitr z path Anat, 1889, vi, 133

65 Eisenlohr Zur Entwicklung der Schrumpfniere aus acuter Nephritis, Deutsch Med Wchnschr, 1892, xviii, 723

glomerulonephritis has been described before by Councilman[17] and others On account of the presence of this substance, I have appended the list of these cases to the list of large white kidneys with amyloid degeneration, and neither macroscopically nor microscopically is there a sharp line of division between them With the same degree of propriety, however, this series could be looked on as a continuation of the series of cases of acute and subacute glomerulonephritis The amount of amyloid-like substance and the degree of typical glomerulonephritis exhibited varies considerably in the different cases A more detailed description may be found in the second part of Table 7

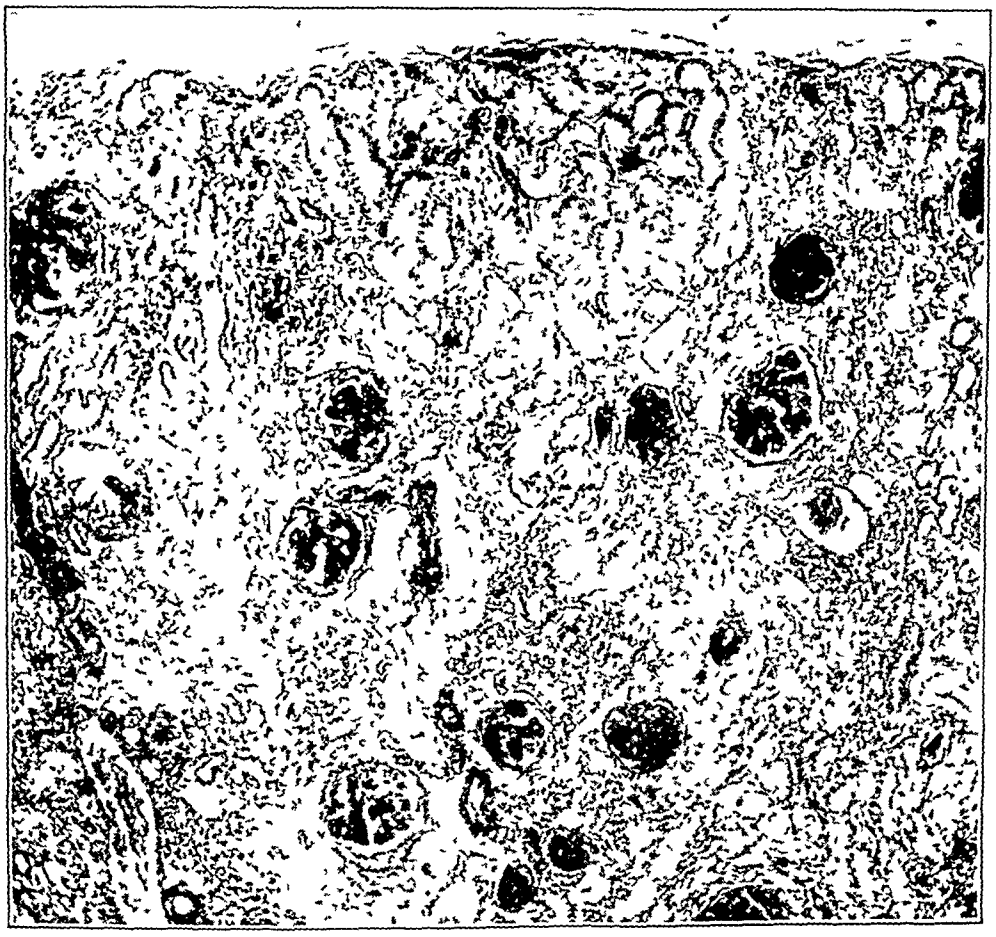

Fig 11 —50x VIII-22 Parenchymatous nephritis and amyloid Secondary contracted kidney Little local amyloid Marked glomerulonephritis Marked diffuse interstitial lesions Obscure sepsis

In all cases there are blood and leukocytes in the tubules, the epithelial degenerations are well marked and casts are more or less abundant

It is only natural that in these very chronic cases the relation to the original sepsis is not so clear as in the more acute cases of glomerulonephritis and of large white kidneys In one case there existed a chronic leg ulcer (Case 22), in another there is a history of scarlet fever (Case 26), and in a third a history of attacks of articular rheumatism In the others, I have surmised the existence of an obscure sepsis on

TABLE 7.—CHRONIC PARENCHYMATOUS NEPHRITIS

Number and Age	Probable Cause	Extent of Amyloid	Heart	Blood Vessels
1 VII 8 10 yrs	Multiple angiosarcoma of bones, chronic suppurative cystitis and pyelonephritis	Spleen, kidneys liver	Normal	Normal
2 XII 16 old man	Chronic tuberculosis of lungs	Spleen kidneys liver	Brown atrophy	Slight atheroma of aorta
3 IX 70 50 yrs	Chronic morphinism, chronic sepsis	Spleen kidneys, liver	⅔ normal	Normal
4 II 4 31 yrs	Chronic pulmonary tuberculosis	Spleen kidneys liver and intestines	Atrophic	Normal
5 XIII 28 30 yrs	Chronic pulmonary tuberculosis	Spleen kidneys, adrenals, liver	¾ normal	Slight atheroma of aorta
6 VIII 13 17 yrs	Subacute pulmonary tuberculosis	Spleen, kidneys	Small	Small
7 VII 89 70 yrs	Carcinoma of bronchus bronchiectatic cavity and chronic pneumonia	Spleen kidneys, liver	¾ normal	Moderate atheroma of aorta
8 IV-37 48 yrs	Syphiloma of liver, syphilitic cirrhosis	Spleen, kidneys, scars in testes	Atrophic	Normal
9 VIII-88 Middle age	Cirrhosis of liver	Spleen, kidneys	1½ times normal	Slight atheroma of aorta, some general arteriosclerosis
10 I 122 35 yrs	Cirrhosis of liver sepsis suspected but not proved	Spleen, adrenals kidneys, intestines	Normal	Normal
11 V-1 45 yrs	Chronic pulmonary tuberculosis	Spleen kidneys liver, intestines	Atrophic	Normal
12 VII-67 52 yrs	Chronic pulmonary tuberculosis	Spleen, kidneys	¾ normal	Normal
13 V-34 50 yrs	Cirrhosis of liver, sepsis suspected but not proved	Spleen kidneys, liver	Brown atrophy	Moderate atheroma of aorta
14 VI-87 38 yrs	Chronic pulmonary tuberculosis	Spleen, adrenals, kidneys	¾ normal size	Atrophic
15 XIII 6 34 yrs	Chronic pulmonary tuberculosis	Spleen, kidneys adrenals, intestines, etc	¾ normal	Slight atheroma of aorta
16 VIII 94 Middle age	Chronic pulmonary tuberculosis	Spleen kidneys, liver	Brown atrophy	Slight atheroma of aorta
17 VII-94	Chronic empyema	Kidneys only	Normal	Marked general arteriosclerosis

AMYLOID DEGENERATION I LARGE WHITE KIDNEYS

Kidneys Gross Appearance	Kidneys Microscopic Lesions
Chronic septic kidney, gravel in right, stone in left renal pelvis	No arteriosclerosis, considerable amyloid in glomeruli, marked fatty and granular degeneration of epithelium, many casts, no new-formed connective tissue, except around abscesses
Slightly enlarged, capsule adherent, surface rough, cortex wide, opaque	Large arteriosclerotic scars, little amyloid in glomeruli, granular and beginning fatty degeneration of epithelium, few casts, slight diffuse growth of cellular connective tissue
11½ × 5½ × 4 cm, cyanotic with opaque spots	Few small arteriosclerotic scars, considerable amyloid in glomeruli, marked granular degeneration of epithelium, many casts, slight diffuse growth of cellular connective tissue
14¼ × 9 × 4 cm, surface smooth, mottled, cortex wide, opaque, full of yellow spots	No arteriosclerosis, much amyloid in glomeruli, marked vacuolization, granular and fatty degeneration of epithelium, many casts, many leukocytes in tubules and tissue, little connective tissue
14×7½×4½ cm, surface smooth, cortex wide, opaque	No arteriosclerosis, much amyloid in glomeruli, much granular and fatty degeneration of epithelium, very many casts, slight diffuse growth of cellular connective tissue
13×5½×3½ cm, surface smooth, cortex wide, pale, opaque	No arteriosclerosis, little amyloid in glomeruli, beginning granular degeneration of epithelium, few casts, moderate growth of cellular connective tissue
13½ × 6 × 3½ cm, cortex wide, opaque	Few small arteriosclerotic scars, moderate amount of amyloid in glomeruli, marked granular degeneration of epithelium, few casts, slight diffuse growth of cellular connective tissue
14½×7×3½, capsule slightly adherent, cortex wide, opaque	Few arteriosclerotic scars, little amyloid in glomeruli, slight glomerulonephritis, fatty degeneration, necrosis and desquamation of epithelium, few casts, slight diffuse growth of cellular connective tissue
13×7½×3 cm, capsule adherent, surface granular, cortex wide, opaque	Few arteriosclerotic scars, much amyloid in glomeruli, subacute glomerulonephritis, much granular and fatty degeneration of epithelium, much pigment, few casts, much new-formed, partly fibrous connective tissue
13½×9×5½ cm, surface smooth, mottled, cortex wide, full of yellow spots	Slight arteriosclerosis, much amyloid in glomeruli, slight glomerulonephritis, extreme granular and some fatty degeneration of epithelium, many casts, leukocytes in some tubules, much new-formed fibrous connective tissue
12½ × 6½ × 4½, cortex opaque	Few arteriosclerotic scars, much amyloid in glomeruli, slight glomerulonephritis, much granular and fatty degeneration of epithelium, very many casts, blood and leukocytes in tubules, much new-formed connective tissue
13 × 6½ × 4, surface granular, cortex opaque	Few arteriosclerotic scars, much amyloid in glomeruli, subacute glomerulonephritis, much granular and fatty degeneration of epithelium, very many casts, leukocytes and blood in tubules, much new-formed connective tissue
12½ × 6 × 4, surface granular, cortex wide, opaque, with cyanotic spots	Many arteriosclerotic scars, much amyloid in glomeruli, subacute and beginning chronic glomerulonephritis, much granular and fatty degeneration in tubules, very many casts, blood and leukocytes in many tubules, much new-formed connective tissue
14½×8×5 cm, surface somewhat rough, cortex wide, opaque	No arteriosclerosis, much amyloid in glomeruli, subacute and chronic glomerulonephritis, much granular and fatty degeneration of epithelium, very many casts, blood and leukocytes in tubules, much new-formed dense fibrous tissue
14×7½×5 cm, capsule adherent, small, retracted, purple scars, cortex wide, opaque	Slight arteriosclerosis, much amyloid in glomeruli, subacute and chronic glomerulonephritis, much fatty degeneration in epithelium, very many casts, blood and leukocytes in tubules, much new-formed connective tissue
14 × 7 × 4 cm, capsule adherent, surface granular, cortex opaque, rather narrow	No arteriosclerosis, much amyloid in glomeruli, subacute and chronic glomerulonephritis, much granular and fatty degeneration of epithelium, very many casts, blood and leukocytes in tubules, much new-formed connective tissue
13⅔×5×3½ cm, capsule adherent, cortex wide, opaque	Moderate arteriosclerosis, few hyaline glomeruli, much amyloid in glomeruli, subacute and chronic glomerulonephritis, much fatty degeneration and necrosis of epithelium, few casts, much new-formed dense fibrous tisue

account of the evidences of sepsis in the kidneys and also on account of the intimate relation of chronic sepsis with the more acute cases out of which these secondary contracted kidneys evidently develop It will be interesting to see whether in the future the relation of these cases to certain septic processes can be established by direct evidence

The overgrowth of the interstitial tissue is very well marked, much more so than in the ordinary arteriosclerotic kidneys and the evidences of

TABLE 7.—Continued CHRONIC PARENCHYMATOUS NEPHRITIS AND AMYLOID DEGENERATION II SECONDARY CONTRACTED KIDNEYS

Number and Age	Probable Cause	Extent of Amyloid	Heart	Blood Vessels
18 V-17 63 yrs	Syphilis, sepsis suspected but not proved	Spleen and kidneys	1½ times normal	Marked atheroma of aorta with aneurysm of arch
19 VII 61 51 yrs	Cirrhosis of liver, sepsis suspected but not proved	Kidneys only	Normal	Moderate atheroma of aorta
20 VIII 47 24 yrs	Sepsis suspected but not proved	Kidneys only	Normal	Normal
21 VIII-22	Sepsis suspected but not proved	Kidneys only	Slight hypertrophy and dilatation of left ventricle	Slight general arteriosclerosis
22 VII 85 Old man	Chronic leg ulcer	Spleen adrenals, kidneys	Brown atrophy	Normal
23 V-50 Middle age painter	Sepsis suspected but not proved	Kidneys and possibly spleen	1¼ times normal	Very marked general arteriosclerosis
24 VII 39 39 yrs	Sepsis suspected but not proved	Kidneys only	1½ times normal	Slight atheroma of aorta
25 XII 57 43 yrs	Sepsis suspected but not proved	Kidneys only	1¼ times normal, marked concentric hypertrophy of left ventricle	Slight arteriosclerosis
26 VI-14 45 yrs	History of scarlet fever sepsis suspected but not proved	Kidneys only	2 times normal	Slight atheroma of aorta, moderate peritoneal arteriosclerosis
27 VI 60 54 yrs	Sepsis suspected but not proved	Kidneys only	3 times normal	Slight atheroma of aorta
28 XIII-110 38 yrs	History of articular rheumatism, sepsis suspected but not proved	Kidneys only	Very large marked hypertrophy of left ventricle	Slight atheroma of aorta

shrinkage are unmistakable I give several illustrations of this type of renal lesion as it is not as well known as the others

Fig 10 (Case 20, VIII-47) shows a condition very similar to that which occurs in old amyloid kidneys, only to an exaggerated degree

Fig 11 (Case 21, VIII-22) belongs more properly to the chronic glomerulonephritis, still there is much of the amyloid-like material in the glomeruli

Fig 12 (Case 24, VII-39) is taken from a kidney with very marked fibrous proliferation of the interstitial tissue and very marked shrinkage The glomerulonephritis is well marked

Kidneys Gross Appearance	Kidneys Microscopic Lesions
12×7×4½ cm , surface somewhat rough , large scar in right kidney , cortex wide, opaque	Marked arteriosclerosis , much amyloid in glomeruli , subacute and chronic glomerulonephritis , much granular and fatty degeneration , necrosis of epithelium , very many casts , some leukocytes in tubules , much new-formed, partly cellular, partly fibrous connective tissue
11½×6½×3 cm , capsule adherent , surface finely granular , few large scars , cortex reduced, purple, full of yellow spots	Marked arteriosclerosis , little amyloid in glomeruli , marked subacute and chronic glomerulonephritis , much fatty degeneration and desquamation in epithelium , many casts , blood and leukocytes in tubules , much new-formed fibrous tissue
8 × 4 × 3 cm , capsule adherent, very irregular shape, pale , cortex much reduced, almost white	Little arteriosclerosis , little amyloid in glomeruli , marked subacute and chronic glomerulonephritis , many casts , blood and leukocytes in tubules , very marked diffuse new formation of connective tissue with shrinkage
11½×5½×2½ cm , surface somewhat granular , cortex opaque, full of yellow spots	Marked arteriosclerosis , much amyloid in glomeruli , marked subacute and chronic glomerulonephritis , much granular and fatty degeneration of epithelium , many casts , much blood and leukocytes in tubules , much new-formed connect tissue with shrinkage
8½ × 3 × 4½ cm , capsule thick , surface coarsely granular, mottled , cortex much reduced	Very marked arteriosclerosis , much amyloid in glomeruli , marked subacute and chronic glomerulonephritis , much fatty degeneration of epithelium , very many casts , many leukocytes in tubules , much new-formed connective tissue with shrinkage
10½×5½×3½ cm , slightly granular, mottled , cortex about 4 mm wide	Marked arteriosclerosis , some hyaline glomeruli , moderate amount of amyloid in glomeruli , subacute and chronic glomerulonephritis , much granular and fatty degeneration of epithelium , very many casts , blood and leukocytes in tubules , thrombosis and leukocytosis in blood-vessels , much new-formed connect tissue with shrinkage
Left, 12½×3½ cm , right, 9×5×2¼ cm , granular, mottled; many small cysts in left kidney	Marked arteriosclerosis , moderate amount of amyloid in glomeruli , subacute and chr , much granular and fatty degeneration of ts , leukocytes in tubules , very much new-formed connective tissue with shrinkage
Moderate size , capsule adherent , surface granular , many hemorrhages , many yellow spots in cortex, which is reduced in size , large uric acid calculi in both renal pelves	Marked arteriosclerosis , much amyloid in glomeruli , marked subacute and chronic glomerulonephritis , marked granular fatty degeneration and necrosis of epithelium , many casts , much blood and some leukocytes in tubules , much new-formed connective tissue with shrinkage
13 × 5 × 3 cm , surface granular , cortex reduced, shows some hyperemic spots	Moderate arteriosclerosis , moderate amount of amyloid in glomeruli , marked subacute and chronic glomerulonephritis , some granular and much fatty degeneration of epithelium , very many casts , leukocytes in tubules , much new-formed connective tissue with shrinkage
9½ × 4½ × 3 cm , surface granular , cortex much reduced	Extreme arteriosclerosis , moderate amount of amyloid in glomeruli , marked subacute and chronic glomerulonephritis , many casts , much blood and some leukocytes in tubules , much new-formed connective tissue with fatty degeneration and shrinkage
⅔ normal surface granular, pale, with reddish patches , cortex thin, hard many calcareous (?) infarctions in pyramids	Moderate arteriosclerosis , much amyloid in shrunken glomeruli , marked chronic glomerulonephritis , fatty degeneration in atrophied and in few remaining large tubules , many casts , blood and leukocytes in tubules , very much new formed connective tissue with much shrinkage

There is nothing in the gross appearance of these kidneys which would permit one to make a diagnosis of the condition with certainty They are neither all typical white contracted kidneys nor is the peculiar coarsely lobulated appearance, described by others, at all pathognomonic for this condition The presence of visible hemorrhages as in Case 25, XII-57, might be suggestive, as they are not so apt to occur in arteriosclerotic contracted kidneys, but it is only on careful microscopic examination that a definite decision can be reached Then the presence of the amyloid-like material in the glomeruli, the evidences of subacute and chronic glomerulonephritis the pronounced and somewhat peculiar

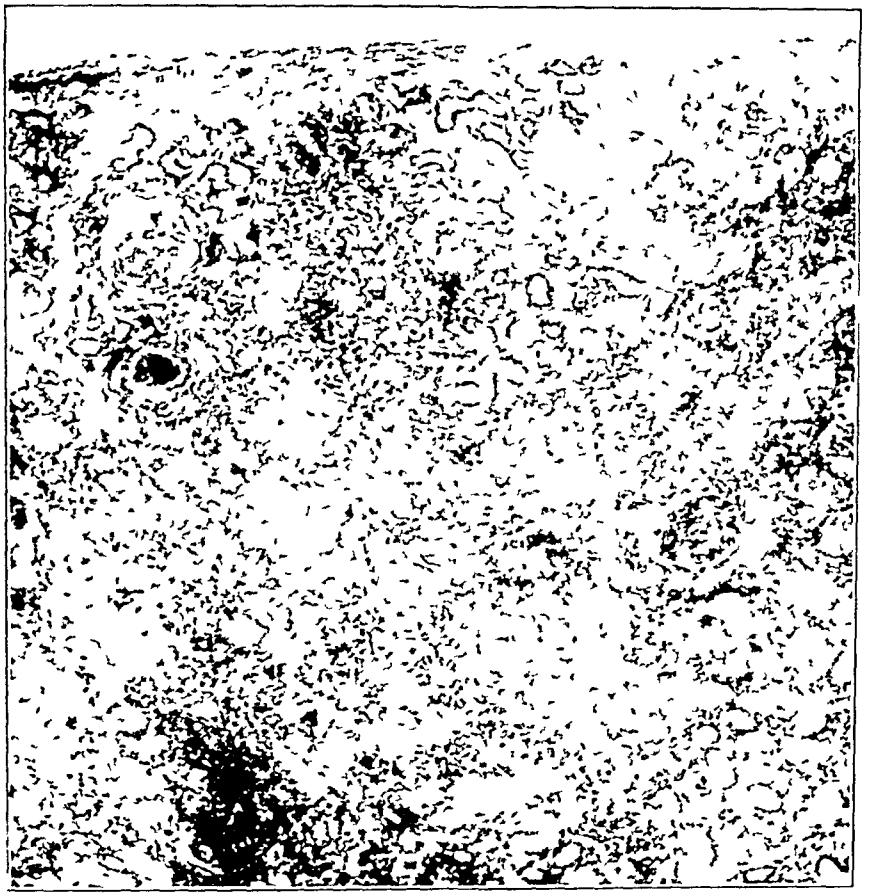

Fig 12—50× VII 39 Parenchymatous nephritis and amyloid Secondary contracted kidney Little local amyloid Marked glomerulonephritis Extreme diffuse interstitial lesions Obscure sepsis

degenerative changes in the epithelium the many casts, and the presence of blood and leukocytes in the tubules will help to settle the differential diagnosis

The relation of this condition, which is evidently primarily renal, to heart and blood-vessels is naturally of particular interest It is quite frequently associated with arteriosclerosis both in the kidneys and elsewhere If we look over the records, we find marked and sometimes extreme arteriosclerosis in the kidneys in all, except in one case (Case 20

VIII-47) General arteriosclerosis is much less common In two cases the aorta and the peripheral blood-vessels are normal, there are slight lesions in six cases, leaving three only in which there is well-marked atheroma of the aorta or peripheral arteriosclerosis or both In one case, in a syphilitic, there is an aneurysm of the arch-

It almost looks as if the arteriosclerosis in the kidneys was secondary to the chronic inflammation in the tissues, as has been suggested repeatedly This interpretation, however, could not be accepted if with Jores we distinguish sharply between true arteriosclerosis and the endarteritis obliterans which accompanies chronic inflammatory processes, because in these cases there is marked splitting up of the internal elastic membrane in the intimal thickening which, according to Jores,[63] would rule out local inflammation as a cause of it I am not quite convinced, however, that this distinction drawn by Jores is entirely justified

We might also explain the comparative rarity of general arteriosclerosis by assuming that it develops late following the full development of the condition in the kidneys

These are surmises, purely, and I believe that the latter has somewhat less ground to stand on than the former

The condition of the heart also varies very much In one case there is brown atrophy, in five cases the heart is only moderately enlarged and in the last three cases only, which, however, represent the extremes of the process, the hypertrophy of the heart is at all considerable

I submit that if it is difficult in arteriosclerotic kidneys to unravel the threads which bind these peculiarly associated conditions together, it is still more difficult to do so in the case of secondary contracted kidneys We can again gather an obscure suggestion that there may be some relation between destruction of kidney-tissue and the development of cardiac hypertrophy, directly or indirectly, but what the relation is seems still very much unsettled The renal lesions, however, evidently must be very extensive to become effective, which corresponds somewhat with the results of experimental research and is also confirmed by observation in those cases in which the kidneys are destroyed by ascending non-suppurative nephritis, for instance, in cases of chronic cystitis and pyelitis following prostatic hypertrophy, of renal calculi and of malignant tumors in prostate and cervix uteri It has been repeatedly pointed out, and it is also borne out by my personal observations, that in such cases we may have much destruction of renal tissue and very marked shrinkage of the kidneys, without any cardiac hypertrophy I have collected reports of eight such cases among my records (see Table 8), and only in one is there the slightest evidence of any hypertrophy In this case, the heart was stated to be one and one-fourth times normal in size, truly, not a very striking change

It is from the experiment that we must hope for the solution of all these grave problems, but the experiment alone will not guide us, unless it is supplemented by sound knowledge of the conditions as they actually exist in man

CONCLUSIONS

The following would be a short summary of my conclusions

At the present time, in many cases entirely too much attention is paid to the kidneys, clinically and anatomically

The so-called primary or genuine contracted kidney represents a disease of the kidney which is the result of arteriosclerosis in the terminal arterioles in this organ, is closely associated with general arteriosclerosis and cannot be properly understood without due consideration of this fact

It is difficult to decide the exact interrelation between the renal lesions, general arteriosclerosis, and the hypertension and cardiac hyper-

TABLE 8.—ASCENDING SUBACUTE AND CHRONIC NEPHRITIS

Number and Age	Other Lesions	Heart	Blood Vessels
1 XIII 105 70 yrs	Carcinoma of rectum extending into bladder, nodular hypertrophy of prostate	Brown atrophy	Slight atheroma of aorta
2 V 44 64 yrs	Death from cerebral embolism, purulent cystitis	Fatty heart	Normal
3 XIII-78 60 yrs	Nodular hypertrophy of prostate gangrenous cystitis, small papilloma of bladder	Normal	Moderate atheroma of aorta
4 1 103 47 yrs	Diverticula of bladder gravel in right renal pelvis, hydronephrosis on left side	Hypertrophy resulting from valvular disease	Marked atheroma of aorta and of aortic valves
5 XIII-39 Extremely stout woman 45 yrs	Death from streptococcus peritonitis following strangulation of intestine	Small with much fatty infiltration	Slight atheroma of aorta
6 XIII 99 Woman 30 yrs	Chronic bronchitis and bronchiectases, fibrinopurulent pleurisy on left side	Soft, flabby	Normal
7 VIII 86 Woman	Extensive malignant epithelioma of cervix with metastases	Slight hypertrophy of left ventricle	Slight atheroma of aorta
8 XIII 37 Old man	Chronic suppurative cystitis, ureteritis, abscesses in prostate, edema of legs, penis and scrotum, beginning cyanotic atrophy of liver	1¼ normal, hypertrophy and dilatation on both sides	Slight atheroma of aorta

Eight cases of ascending subacute and chronic nephritis, in four cases very extensive destruction of kidney tissue of which two show marked cardiac hypertrophy In the last case there is in addition evidence of cardiac insufficiency

trophy which is usually present in these cases It is only safe to say that the rôle of the kidney lesions in the production of the hypertension has been evidently considerably exaggerated

There is some reason to believe that the condition as a whole is a toxic one So far, however, lead is the only substance which seems to bear any definite etiological relation to the general process

Of true primary subacute and chronic inflammations of the kidneys there remain subacute and chronic glomerulonephritis, definitely in the majority of instances due to chronic sepsis

Closely related to this, etiologically and anatomically, is the subacute and chronic amyloid kidney (the large white kidney of other authors)

From a combination of these last two conditions there arises the so-called secondary contracted kidney which in our series was responsible for eleven out of thirty-seven cases of seriously contracted kidneys,

Kidneys Gross Appearance	Kidneys Microscopic Lesions
Large soft, surface finely granular, mottled, cortex reduced in places, opaque, marking indefinite	Large arteriosclerotic scars, in some sections large areas of cellular infiltration and new formation of cellular connective tissue, much fatty degeneration in tubules and connective tissue, leukocytes in tubules
Left, 11×4×3½, right, 10×5×3 cm, large flat scars on surface	Some arteriosclerotic scars, marked diffuse thickening of interstitial tissue
Two thirds normal size, surface rough, with purple scars, cortex reduced	Marked arteriosclerosis, few arteriosclerotic scars, marked diffuse somewhat irregular fibrous thickening of interstitial tissue with some cellular infiltration, atrophy of tubules in worst places
Left 9 × 4 × 5½, surface granular, with many large retracted scars, some hydronephrosis, right kidney, 11×5½×4, similar changes but less marked gravel in pelvis	Little arteriosclerosis, few hyaline glomeruli, large areas of cellular infiltration and new formation of fibrous tissue with collapse of tubules, marked fibrous thickening of capsules of glomeruli, blood in tubules, few casts
7½ × 3½ × 2½, granular, gray and red, cortex narrow, full of bright yellow glistening spots, renal pelves filled completely with uric acid stones	Moderate arteriosclerosis, some arteriosclerotic scars, very marked cellular infiltration and diffuse new-formation of dense fibrous tissue with collapse of tubules, urates in dilated tubules in pyramids and in cortex
Renal calculus on left side, with pyonephrosis and almost complete destruction of left kidney, chronic pyelonephritis on right, also with very extensive destruction	Much new-formed cellular connective tissue with marked shrinkage, small remnants of kidney tissue
Purulent pyelonephritis with dilated pelves	Moderate arteriosclerosis, some arteriosclerotic scars, suppuration in and around ducts in papillæ, very marked diffuse cellular infiltration and new formation of dense fibrous tissue throughout medulla and cortex, with collapse of majority of tubules and compensatory hypertrophy of rest, leukocytes in many tubules
7½ × 4 × 2½ cm, capsule adherent, surface coarsely nodular, many large, deep and retracted scars, cortex much reduced, markings poor, renal pelves dilated many pyramids obliterated	Marked arteriosclerosis, few hyaline glomeruli, very marked diffuse cellular infiltration with almost complete collapse of tubules compensatory hypertrophy of rest, leukocytes in few tubules, fibrous thickening of capsules of glomeruli

The etiology of the cases of secondary contracted kidney is not quite so clear as that of the more acute conditions but it is highly probable that chronic sepsis, in the broadest sense, is an important factor

The lesions in subacute and glomerulonephritis and secondary contracted kidneys are practically always hemorrhagic, and in subacute and chronic amyloid kidneys frequently so

The interstitial lesions which are present in these latter conditions begin to develop early practically simultaneously with the epithelial lesions It is not very likely, therefore, that they should be secondary to them

A PNEUMOGRAPHIC STUDY OF RESPIRATORY IRREGULARITIES IN MENINGITIS*

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It has long been common knowledge that irregularities in respiratory rhythm were occasionally to be seen in meningitis In general, however, these respiratory irregularities have been regarded as of much less frequent occurrence and as of much less diagnostic significance than irregularities of the pulse and heart action In most writings on the subject of meningitis, these respiratory symptoms are either not mentioned at all or are referred to only briefly and casually, the usual statement being that the Cheyne-Stokes type of breathing is sometimes seen toward the end of the disease By certain of the earlier writers, however, especially among the French, the disturbances of respiration were recognized as of common occurrence and were described at some length

Biot,[1] in 1878, writing on the subject of Cheyne-Stokes breathing devotes several pages to quotations from various authors, which show that they regarded the disturbances of respiration as common and important symptoms in meningitis Biot's purpose, in these quotations, was to furnish support for his contention that the characteristic respiratory change in meningitis was not the true Cheyne-Stokes type of breathing, although it was frequently marked by apneic pauses According to Biot, the "meningitic rhythm" lacked the rhythmical alternation of periods of apnea and periods of gradually increasing and decreasing respiratory movements, which is the essential feature of the Cheyne-Stokes type The respiratory pauses occurred at irregular intervals and the individual respirations showed constant irregularity in size and in rate

Since Biot's writings the subject of the respiratory symptoms of meningitis has apparently received little attention It has seemed to us worth while, therefore, to study graphically the respiratory movements in a considerable number of cases of meningitis with a view to determining the frequency and the character of these changes

METHOD

Various forms of instruments have been used for registering the movements of respiration The type that we have found the simplest,

*From the Medical Service of the New York Hospital

1 Biot Etude clinique et expérimentale sur la respiration de Cheyne Stokes Paris, 1878

and at the same time the most satisfactory, is the familiar spiral-spring pneumograph of Marey, which consists of a spiral spring 12 to 15 inches long enclosed in a thin rubber tube The tube is closed at each end by means of a stopper to which the ends of the spring are attached, and an opening in one stopper affords the only opportunity for the entrance or escape of air This air-chamber is connected by rubber tubing with a tambour and writing lever By straps attached to each end the tube is stretched lightly about the chest or upper abdomen so that changes in the circumference of the thorax or abdomen produce a corresponding change in the air-pressure in the closed system of tubes Thus the expansion of the chest or the descent of the diaphragm will cause an elongation of the pneumograph with rarefaction of the air within and a corresponding sinking of the tambour and writing lever Conversely the expiratory collapse of the chest or abdomen will result in an elevation of the tambour and of the lever

In order to study both the thoracic and the diaphragmatic mechanism of respiration two pneumographs were used always one placed about the chest at the level of the third rib the other about the abdomen midway between the ensiform cartilage and the umbilicus

In all the illustrations the movements of the thorax are recorded in the upper tracing, those of the diaphragm in the lower one In each the *descending* limb of the trace marks the *inspiratory* movement, the ascending limb the expiratory movement

In taking the tracings care was exercised always to avoid alterations in the type of respiration due to conscious and voluntary breathing and to prevent errors caused by convulsive movements, crying, coughing etc

By making it a rule always to observe the respirations for some minutes before applying the pneumographs, it was possible to tell whether the applications of the instruments produced any change in the character of the breathing

NORMAL RESPIRATORY MOVEMENTS

In the consideration of disturbances of the respiratory movements, it is essential to a clear understanding of the matter that one keep in mind the three fundamental functions which determine all such movements, viz, rhythm (rate), force (amplitude), and tonicity of the respiratory muscles[2] It is important also to realize, as Mosso[3] has so clearly shown, that these three functions are quite independent of each other and that their reciprocal relations are by no means constant and unchangeable A further important fact is that, in the case of the last two of these functions at least, this same independence exists in the movements of the

2 In tracings of respiratory movements changes in muscular tonus are shown by changes in the general level of the trace

3 Mosso Les mouvements respiratoires du thorax et du diaphragme, Arch ital de biol, 1903, xl, 43

thorax as compared with those of the diaphragm and the abdominal muscles For example, one may see, in the movements of the diaphragm, rhythmical variations in the force or in the muscular tonus, or in both, while the movements of the thorax are perfectly uniform in both of these respects

Although it may be said that in normal individuals, both adults and children, the respiratory movements are usually quite regular in rhythm, amplitude and muscular tonus, it has been shown by Mosso[4] and others

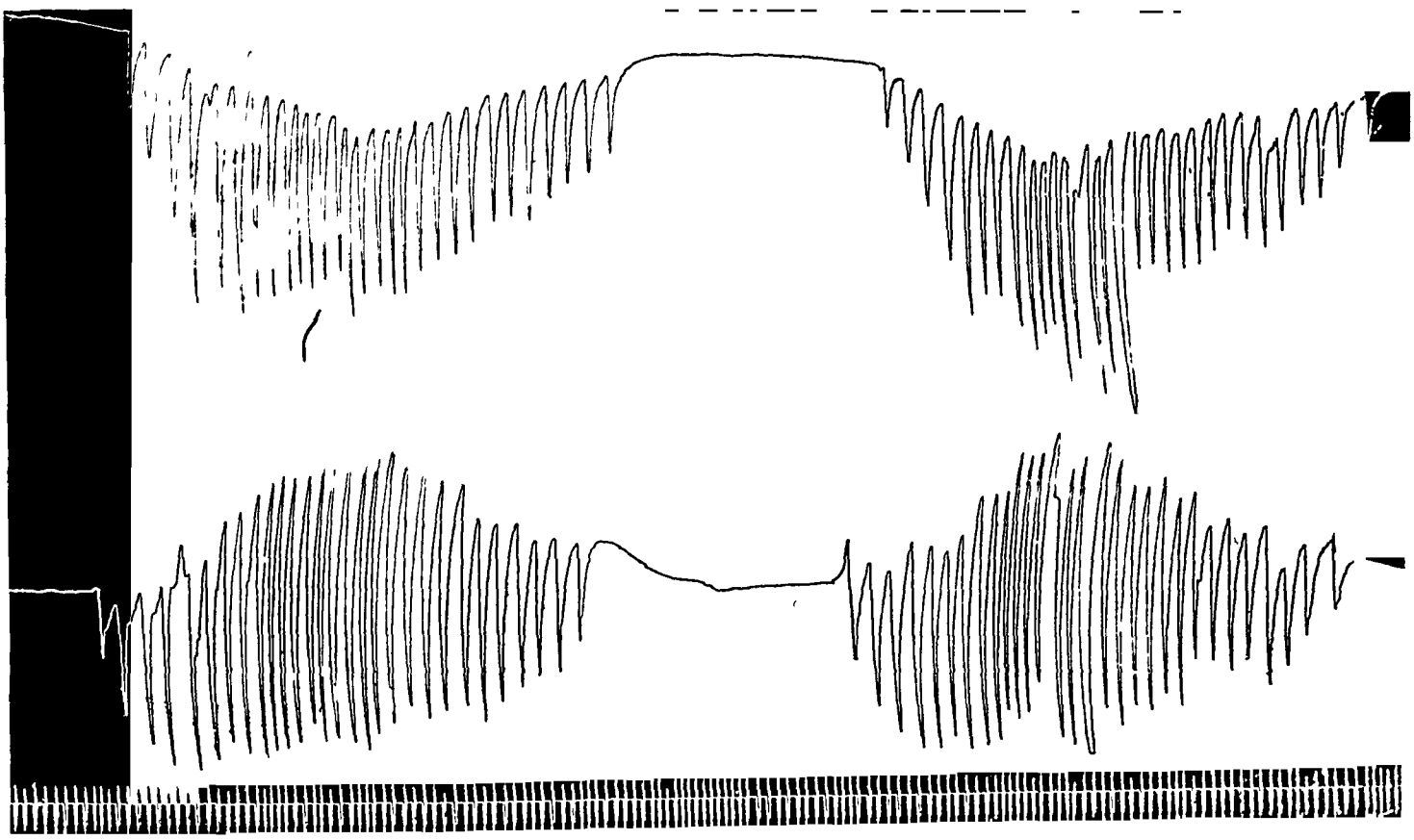

Fig 1—An example of the adult type of Cheyne Stokes breathing, showing the large number of respirations in each period, the relatively short apneic pause and the high levels reached by the expiratory up strokes in the abdominal trace In this and the following tracings the upper line represents the thoracic tracing, the middle line, the abdominal tracing, and the bottom line, the time in seconds The down strokes record the inspiratory movements

that in the state of complete repose, and especially during sleep, the respirations tend to assume a certain undulatory variation in amplitude That is to say, the depth of successive inspirations gradually increases and decreases in a rhythmical way This tendency is most marked in infants and in the aged, but may be seen at all ages Among old people during sleep, these undulations may be so pronounced that during the

4 Mosso La respiration périodique et la respiration superflue ou de luxe Arch ital de biol, 1886, vii, 48

periods of shallow breathing there may be little or no respiratory movement, i e, the breathing may assume the Cheyne-Stokes type In the new-born, respiration is normally quite irregular in all its characters,[5] but this irregularity soon disappears, although the tendency to irregularity, and especially to rhythmical changes in amplitude, is noticeable for two or three years[6]

In all there were studied forty-eight cases of meningitis of various types In five of these the tracings were for one reason or another unsatisfactory and were discarded The remaining forty-three cases form the basis of this paper

Age.—The series included nineteen infants, eleven children over 2 years of age and thirteen adults The youngest was an infant of 2 months, the oldest a woman of 55 years

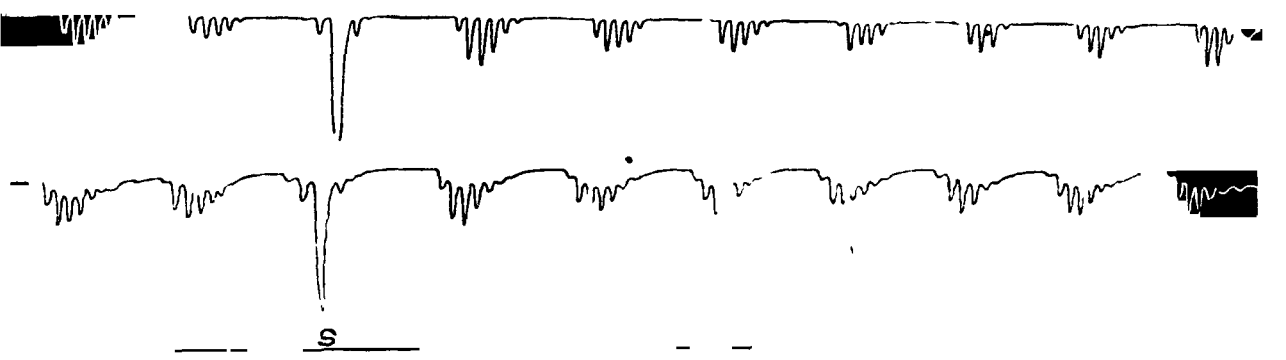

Fig 2.—Typical example of the infantile type of Cheyne Stokes breathing, in a child of 10 months, showing the small number of respirations in each period, the relatively long pause the absence of high expiratory levels in the respirations and the short duration of the cycles (Each complete cycle occupied eleven seconds) A deep sigh is shown at S

Types of Meningitis.—Among the forty-three cases there were thirty-two of tuberculous meningitis, six of the epidemic cerebrospinal type, four of secondary streptococcus meningitis and one of acute syphilitic basilar meningitis Of the thirty-two cases of tuberculous meningitis, twenty-four were proved to be such either by autopsy, by the finding of tubercle bacilli in the spinal fluid or by the results of guinea-pig inoculations In the remaining eight cases the diagnosis was not so proved, but the clinical picture was so characteristic that there could be no reasonable doubt as to the diagnosis

The cases were studied usually from the time of their admission to the hospital up to that of their death or recovery This period varied in

5 Vallois and Fleig Le graphique respiratoire chez le nouveau-né, Compt rend de l'Acad de Sciences, 1905, cxl, 1422

6 Gaujoux Contribution a l'étude de la respiration chez l'enfant, Ann d méd et chir infant, 1908, xii, 325

different cases from two days to several weeks During this time respiratory tracings were taken at frequent, usually almost daily, intervals Occasionally, when the disturbances were of unusual interest, tracings were taken several times in the course of a day

As might be expected, the onset and early days of the disease were the portion of the clinical course least often seen and studied, since in most instances the patients were not brought to the hospital until the symptoms had become well established In several instances, however, it was possible to follow the symptoms almost from the onset

In all of the thirty-two cases of tuberculous meningitis respiratory irregularities were observed during some part of the illness and usually throughout the greater part of it Among the eleven non-tuberculous cases alterations in the respiratory rhythm were noticed in all but two cases That is to say, disturbances of respiratory rhythm constituted a symptom in 95 per cent of all cases The two cases which showed no

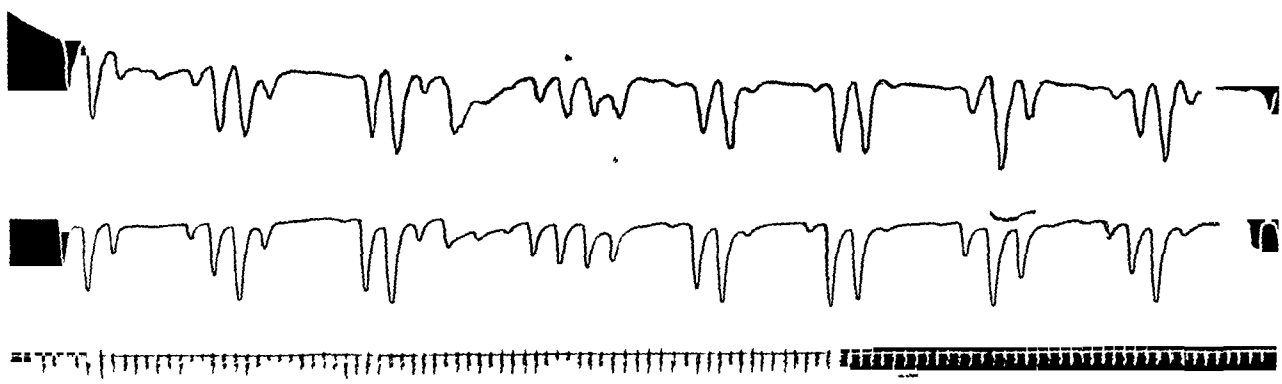

Fig 3—Another example of the infantile type of Cheyne Stokes breathing, seen in a child of 4 years The periods are composed of 2, 3 or 4 respirations

such disturbances were both instances of the epidemic cerebrospinal type One of these a man of 20, was admitted on the third day of his illness, ran a very mild course and recovered within a few days His respirations throughout were quiet, regular and uniform, and showed no change other than a slight increase in rate during the first day or two The other, a child of 7 years, lived for some ten days after admission During most of this time the restlessness and twitchings were so constant as to make it impossible to get satisfactory tracings In the two good tracings that were obtained, however, no irregularity was to be seen

Time of First Appearance of Irregularity—In most cases it was not possible to determine the time of the first appearance of the respiratory symptoms, as the patients were brought to the hospital only after the disease had become well established and the respiratory arhythmia was apparent on admission There is considerable evidence, however, to show that the respiratory irregularities often appear very early in the disease.

especially in those forms of meningitis in which the symptoms develop abruptly and violently Thus they were noticed on the second day of symptoms, in a man with meningococcic meningitis and in another with acute syphilitic basilar meningitis, on the fourth day, in a child with streptococcic meningitis, and, in three children with tuberculous meningitis, on the sixth, seventh and eighth days, respectively

TYPES OF ARHYTHMIA

When one compares a large number of respiratory tracings from cases of meningitis, one is at first struck with the great number and diversity of the variations from the regular and uniform rhythm of normal individuals It soon becomes apparent, however, that these numerous variations can be classified into three fairly distinct groups although the lines of demarkation between these are by no means always sharp and distinct There are

1 The type of Cheyne-Stokes

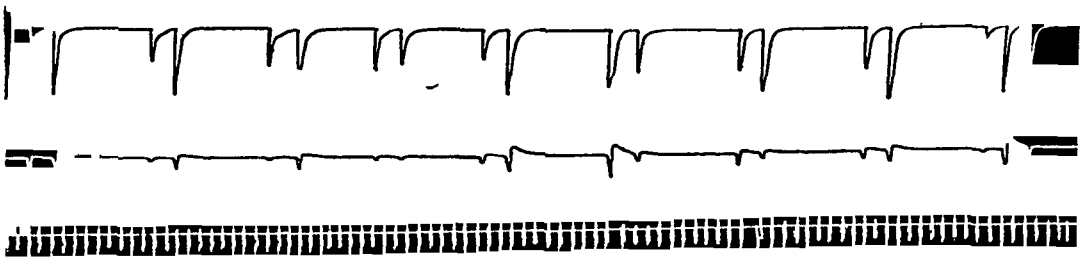

Fig 4 —Tracing from child of 2 years, showing an exaggerated form of the infantile type of Cheyne Stokes breathing An example of the so called "grouped respirations"

2 Biot's meningitic rhythm

3 An undulatory type

Cheyne-Stokes breathing was observed in twenty-three (53 per cent) of the forty-three cases Among the thirteen adult cases it was encountered only four times (30 per cent) Among the thirty infants and children it was of much more frequent occurrence, being met with in nineteen (63 per cent) of the thirty cases This type of disturbance seems to be more prevalent among the cases of tuberculous meningitis It was observed in twenty (62 per cent) of the thirty-two cases of tuberculous meningitis and in three (27 per cent) of the eleven non-tuberculous cases

Before attempting to discuss the special features of Cheyne-Stokes breathing in meningitis and to contrast it with the other types of respiratory irregularity, it may not be amiss to recall briefly the essential features of this type of respiratory disturbance, as it is commonly seen in such conditions as cerebral hemorrhage, uremia and certain forms of heart disease It consists of the rhythmical alternations of periods of respira-

tory movement and periods of apnea All the respiratory periods are of approximately equal length and are made up of about the same number of individual respirations These show first a gradual increase in force and amplitude, the respirations becoming labored and dyspneic, and then a gradual decrease With the waxing and waning of the respirations there is usually also a corresponding slight increase and decrease in the respiratory rate The periods of apnea also are of approximately equal length The duration of the pause differs much in different cases, but is usually from one-half to three-fourths of the time occupied by a respiratory period (Fig 1) The number of respirations to a period varies, in different cases, between fifteen and thirty In an average case the time occupied by a complete cycle would be approximately sixty seconds, the respiratory period being composed of twenty respirations and occupying forty seconds and the period of apnea lasting twenty seconds

The Cheyne-Stokes breathing observed in meningitis in adults shows no essential differences from that seen in other conditions In infants and young children, however, this type of breathing presents certain features which distinguish it sharply from the adult type (Figs 2, 3 and 4) The duration of a complete cycle is very much shorter the average time occupied being only about ten seconds The number of respirations in each period is much smaller, varying from two to eight, the usual number being four or five The time of the period of apnea is relatively long, the pause usually occupying at least as much time as does the respiratory period The force and amplitude of the respiratory movements are naturally much less than in the adult type of breathing, and there is lacking, in most cases, the forcible expiration which, in the adult type, during the period of dyspnea, carries the expiratory limb of the trace high above the expiratory level seen in the periods of apnea

The question at once arises as to whether this special type of Cheyne-Stokes breathing seen in children with meningitis is conditioned on the nature of the disease or merely on the age of the patient, in other words, is it a meningitic type of Cheyne-Stokes breathing or only an infantile type? This question we cannot answer positively We have happened thus far to encounter no cases of Cheyne-Stokes breathing in children or infants in diseases other than meningitis which could be used for comparison Cheyne-Stokes breathing in meningitis in adults, however, shows no special variation from that seen in other diseases, and there is every reason to believe that the special features of the type just described depend not on any particular form of disease, but on the peculiarities of respiration, as it occurs in infants and children We shall therefore, in the future, refer to it as the infantile type of Cheyne-Stokes breathing This infantile type is not confined to young children, it was observed in children whose ages were, respectively, 6, 8, 11 and 12 years On the other

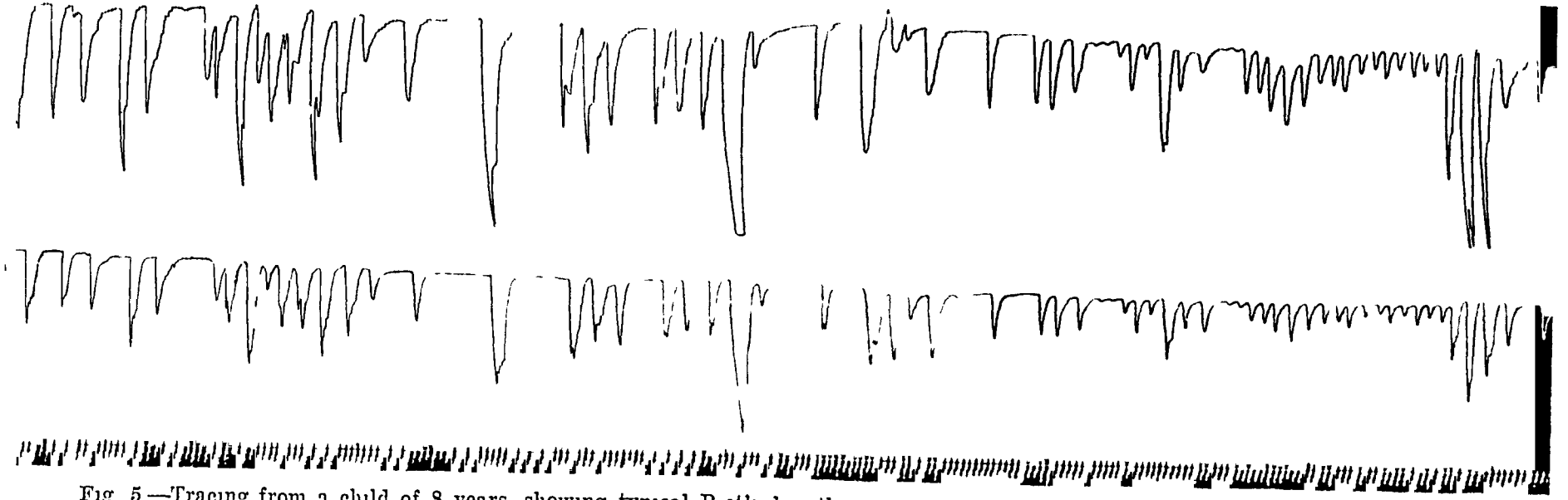

Fig 5 —Tracing from a child of 8 years, showing typical Biot's breathing Note the pauses which occur at irregular intervals and vary in length, the frequent deep sighs, and the constant irregularity of the respirations in force and rhythm

hand, in one child of 8 years, the Cheyne-Stokes breathing approached in character the adult type

"GROUPED RESPIRATIONS"

West[7] in an article on Periodic Respiration, divides this into two special forms

1 Cheyne-Stokes respiration which is characterized by the three features of (a) long pause, (b) the crescendo and diminuendo of the respirations and (c) the rapid rate

2 A form which he calls "grouped respirations" in which "the respirations occur in groups of two, three or four at a time Each respiration is slow and deliberate and of approximately equal depth, while the intervals are rarely longer than ten or perhaps fifteen seconds, so that the rate of respirations is not more than 8 to 10 or 12 in the minute"

These "grouped respirations" he has seen only in meningitis and generally in the posterior basic form These two forms of periodic respiration, he believes, "stand in marked contrast with one another, not only clinically, but also in prognostic significance" It seems hardly possible that West's "grouped respirations" can be anything else than the infantile type of Cheyne-Stokes, although he does not mention the age of the patients in which this type of breathing has been observed In the more extreme examples of the infantile Cheyne-Stokes it is usual to have only two, three or four respirations to each cycle, and these show no very great difference in amplitude It often happens, however, that in the same tracing there will be a few cycles containing five or six respirations, and then the increase and decrease in amplitude is much more apparent

West's statement, that "each respiration is slow and deliberate," is difficult to accept While it is true that with only two or three respirations to a cycle the number of respirations per minute may be only ten or twelve, yet these few respirations occupy only a small portion of the time of the cycle The duration of each respiration, therefore, is very short, usually between one and one and three-fourths seconds, whereas in the adult type of Cheyne-Stokes the duration of each respiration is usually somewhat longer

We feel convinced that the "grouped respirations" are identical with the infantile type of Cheyne-Stokes, and we cannot, therefore, accept the conclusion of West that this form of periodic respiration differs from Cheyne-Stokes breathing, either clinically or in its prognostic significance Figures 3 and 4 show the more extreme forms of the infantile type of Cheyne-Stokes, which seem to be identical with West's grouped respirations In both of these cases tracings taken at other times have shown the typical form of Cheyne-Stokes breathing

7 Tr Clin Soc, Lond, 1906, xxxix 46

BIOT'S BREATHING

Attention to this type of respiratory arhythmia has been called in a recent article by one of us (Conner) [8] Biot declared that the disturbance of respiratory rhythm so frequently observed in meningitis, while it bore some resemblance to, was by no means identical with true Cheyne-Stokes breathing, as had been assumed by various writers The characteristic features of this "meningitic rhythm," he pointed out, were

1 Periods of apnea of varying length and occurring at irregular intervals

2 Constant irregularity in the rhythm and in the force of the individual respirations

3 The frequent occurrence of deep, sighing respirations

This type of breathing he believed to be characteristic of meningitis and he implied, although he did not state explicitly, that true Cheyne-Stokes respiration does not occur in that disease In this conclusion he was clearly in error for we have already shown that the Cheyne-Stokes

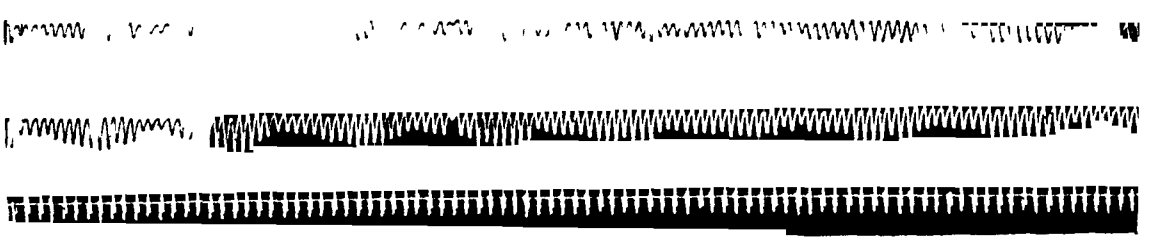

Fig 6—Tracing from a child of 2 years, showing undulatory variations in the force of the inspiratory movements

type is really very common in meningitis, occurring as it did, in 53 per cent of our series of cases In this same series Biot's meningitic type of breathing (Fig 5) was observed in nine cases, or 27 per cent In six instances it was the only type of irregularity noticed In three cases the Cheyne-Stokes type was also present at some time during the illness

The incidence of the Biot type in the tuberculous cases was distinctly less than in the non-tuberculous cases, there being five instances of it among the thirty-two tuberculous cases and four among the eleven non-tuberculous Biot's breathing was observed four times among the thirteen adults or 30 per cent, and five times among the thirty infants and children, 17 per cent

It is interesting to note that whereas the percentage of the Cheyne-Stokes type in children was more than double that in adults, the Biot type was encountered almost twice as frequently in adults as in children

The occurrence of deep sighs is one of the striking and easily recognizable features of this type of arhythmia They vary much in frequency

8 Conner Biot's Breathing, Am Jour Med Sc, 1911, cxli, 350

in different cases, sometimes occurring in rapid succession, sometimes seen only at long intervals Frequently each sigh is followed immediately by an apneic pause of greater or less duration This rule is not constant, however, for occasionally the respirations continue after a sigh without any such interruption On the other hand, the periods of apnea are by no means always preceded by such sighs, not infrequently they are seen to occur in the midst of quiet respirations

These deep, sighing respirations were sometimes observed when the breathing in other respects appeared almost or quite normal They were also seen occasionally in the course of typical Cheyne-Stokes breathing (see Fig 2) They seem to be a very characteristic feature of the breathing of meningitis At least they are, in our experience, rarely met with in diseases other than meningitis

It has been said that in three of the nine cases in which Biot's breath-

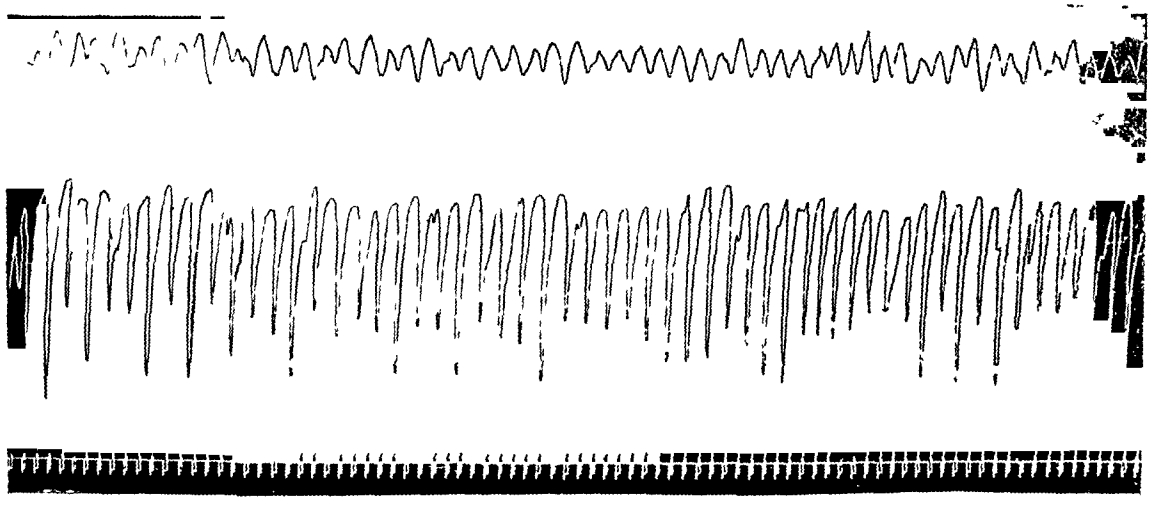

Fig 7—Tracing from a child of 4 months, showing marked variation in the force of the respirations, with a tendency to the alternation of deep and shallow respirations

ing was observed, the Cheyne-Stokes type was also seen at some time in the disease The first patient, a child of 8 years, with tuberculous meningitis, showed typical Cheyne-Stokes breathing when admitted to the hospital on the fourteenth day of the disease During the next two days the breathing became less distinctly Cheyne-Stokes in type and there were many deep sighs Then came a period of three days when the respiration was normal except for slight undulations and occasional sighs, then two days when the breathing was of the Biot type, and then a day or two of very rapid and regular respiration followed by death

In each of the other two patients (children with tuberculous meningitis who entered the hospital about the end of the first week of their illness) Biot's breathing was seen on the day after admission After a day or two the respirations took on the Cheyne-Stokes character, which they retained for several days Then as the breathing became very rapid

just before death, it became quite regular This terminal phase of very rapid and regular breathing was an almost constant feature in our cases of meningitis No matter how extreme and persistent the respiratory arhythmia might have been, there was regularity, just before death, a period varying from a few hours to two or three days, when the respiration became very rapid (50 to 80 per minute) and perfectly regular in both force and rhythm

The scope of this article does not admit of a discussion of the causation of the Biot type of respiration This subject has been considered briefly by one of us (Conner)[8] in the paper on Biot's breathing already cited

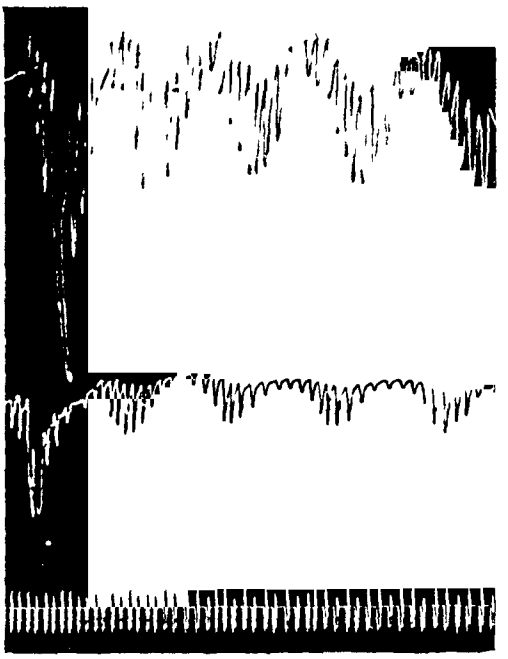

Fig 8—Tracing showing marked undulations in muscular tonus and in force, following a deep sigh Taken from a child 2 years old

THE UNDULATORY TYPE

The third group of respiratory irregularities, which, for lack of a better name, we have called the undulatory type, differs from the other two groups in that the occurrence of periods of apnea does not constitute a feature There were twelve of the forty-three cases in which neither the Cheyne-Stokes nor the Biot type was detected, but in which, nevertheless, the tracings showed a departure from the normal, uniform type

Under this group irregularities of three distinct kinds were observed corresponding to disturbances in the action of each of the three factors of rhythm, force and muscular tonus These were

1 Undulatory variations in the depth of inspiration (disturbances of force or amplitude)

2 Undulatory variations in the general level of the trace, i e, in both the inspiratory and expiratory levels (disturbance of muscular tonus)

3 Rhythmical variations in frequency (disturbance of rate or rhythm)

These undulatory changes in rhythm, force and tonus were seen generally in both the thoracic and abdominal tracings, although frequently they were more pronounced in one than in the other Sometimes, however, one trace would show variations slightly or not at all, while in the other they would be very marked Such undulatory irregularities were by no means confined to the cases included in this group There were, indeed, very few cases which, at some time in the course of the disease, did not show such undulatory variations, but in the twelve cases of this group the respiratory irregularities stopped here and the more striking and obvious forms of disturbance were not seen Undulations in amplitude

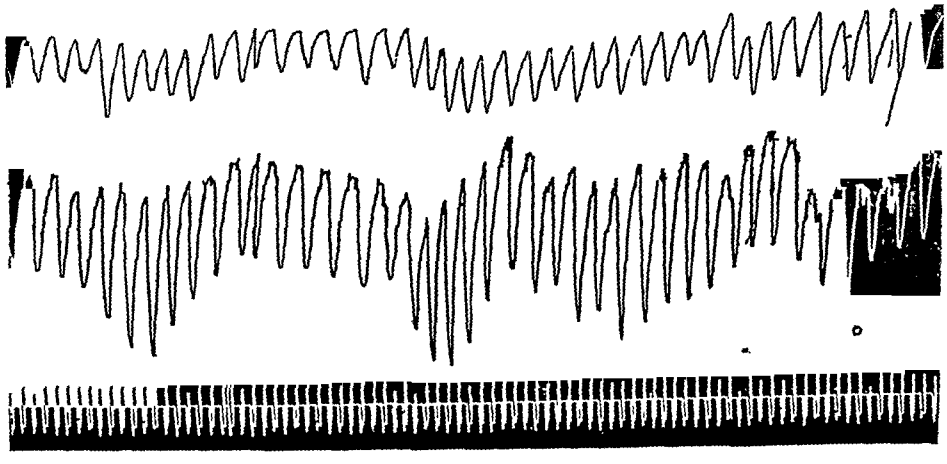

Fig 9—Tracing from a woman of 32 years, showing undulatory variations in force, rate and muscular tonus The increase in rate corresponds with the periods of increase in force

alone seem to represent the mildest and commonest type of disturbance of the respiratory mechanism Indeed, slight variations in amplitude are perfectly normal in young infants, and are frequently seen in the tracings from older persons, especially during sleep

The variations in amplitude were sometimes seen alone, although often they were combined with variations either in tonus or rate, or in both On the other hand, variations in muscular tonus or in rate were almost always associated with undulations in amplitude, the increase in rate always synchronizing with the increase in amplitude Figure 6 shows undulatory changes in amplitude, which are confined almost entirely to the abdominal trace In Figure 7 is seen quite a different sort of disturbance in amplitude The abdominal trace especially shows an interesting alternation of one large with one or two much smaller respirations, and bears a strong resemblance to the tracings of a pulsus alternans

Figures 8 and 9 show distinct undulations in muscular tonus, the disturbances being more pronounced in the thoracic trace in one and in the abdominal trace in the other In both figures the rhythmical change in amplitude is also apparent, and in Figure 9 an increase in rate is seen corresponding with the periods of increased amplitude

THE RELATIONS OF THE DIFFERENT TYPES OF ABNORMAL RESPIRATORY RHYTHM TO EACH OTHER

The undulatory type is unquestionably much the commonest, and, so to speak, the mildest type of respiratory irregularity It was seen in some form and at some time in practically every case of meningitis that was observed for any length of time In those cases in which the gradual development of the Cheyne-Stokes or Biot type could be watched it was always the first indication of disturbed rhythm and in the few cases which recovered it was the last to be seen before the breathing became normal It was often possible, especially in children to follow the gradual change from breathing which showed only slight undulations in the inspiratory level of the trace to the fully developed Cheyne-Stokes type and from this back to the simple undulations The undulatory rhythm was seen often in cases which at other times would show the Biot type of breathing, but in general it seemed to bear a closer relation to the Cheyne-Stokes type It cannot, however be regarded always as merely a rudimentary form of Cheyne-Stokes for in many cases the undulation would vary considerably in length and would lack the complete rhythmical alternation that is so distinctive a feature of the Cheyne-Stokes type

The relationship between Biot's and the Cheyne-Stokes type was discussed by one of us (Conner) in the article on Biot's breathing already referred to,[8] and we quote from it as follows

> Biot was quite warranted, it seems to me in insisting on the sharp distinction between this [his] *meningitic type and the form of breathing described by Cheyne* and Stokes The two types have really little in common The dominant feature of Cheyne Stokes breathing is the rhythmic succession of periods of apnea and periods of dyspnea The apneic pauses in any given case are quite uniform in length and occur at regular intervals The periods of dyspnea are all composed of about the same number of respirations and show regularly a progressive waxing and waning in the force of the respirations The characteristic feature of Biot's type, on the other hand, is its complete lack of any sort of rhythm The periods of apnea vary in length and occur at irregular intervals and there is constant irregularity in both the rate and the force of the individual respirations Such essentially different types of breathing must, it seems to me, have a different cause and pathogenesis The fact that Cheyne Stokes respiration is occasionally seen in patients who, at other times, show Biot's type, only means, I think, that in such patients the intracranial conditions of—let us say—pressure or irritation are changing

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Conner Biot's Breathing, Amer Jour of Med Sciences, 1911, cxli, 350

THE RELATIONS OF RESPIRATORY DISTURBANCES TO THE OTHER SYMPTOMS OF MENINGITIS

Thus far we have been unable to detect any very close relationship between the respiratory irregularities and any of the other prominent symptoms of meningitis Most of the irregularities were observed in patients who, at the time, were in a state of stupor or coma, but there were a number of exceptions to this rule One patient, a man with streptococcus meningitis, was under observation for five weeks before he died Up to the last week of life he was perfectly conscious and rational, although inclined to sleep most of the time, yet this man showed almost constantly throughout his stay in the hospital typical Biot's breathing There were some instances, also, in which Cheyne-Stokes breathing was seen in children who were quite conscious at the time Irregularities in the heart action were not detected in many of our patients, but when met with did not seem to bear any relation to the respiratory irregularities The influence on the respiratory symptoms of the removal of cerebrospinal fluid by lumbar puncture was less distinct than we expected In only one instance did we see Cheyne-Stokes breathing disappear on the removal of *fluid by puncture In another case the breathing, which showed only* slight undulations in amplitude before the puncture, became frankly Cheyne-Stokes in character afterward With these two exceptions no change was noticed as the result of lumbar puncture

THE DIAGNOSTIC VALUE OF RESPIRATORY IRREGULARITIES IN MENINGITIS

From the mere fact that respiratory irregularities were observed in 95 per cent of all the cases of meningitis studied, it is evident that they are to be classed among the common symptoms of that disease Moreover, in most instances, they belong among the easily recognizable symptoms No pneumograph is required for the recognition of the Cheyne-Stokes or the Biot type of breathing, all that is needed is the careful and patient observation of the movements of respiration when the patient is quiet and undisturbed One or the other of these two types was seen in two thirds of all our cases and was usually present throughout most of the course of the disease When the respiratory movements show only undulatory variations, without pauses, the disturbance is less easily detected by the unaided eye, but even this form can often be recognized if the irregularities be at all marked

Of the three types of arhythmia, Biot's is unquestionably the most nearly pathognomonic of meningitis We are not prepared to say that it occurs only in meningitis, but among the tracings of several hundred patients, both adults and children, we have met with it, in its typical form, only in ten cases, and nine of these were proved cases of meningitis The tenth case was that of some intracranial complication of mastoiditis which may have been meningitis, but was not proved to be By some of

the earlier writers this form was sometimes called "cerebral breathing" and was believed to occur in a variety of intracranial affections From our experience we are convinced that its occurrence in conditions other than meningitis must be rare, to say the least The Cheyne-Stokes type of breathing has of course, much less diagnostic significance In the case of adults it probably has no value in distinguishing meningitis from other intracranial diseases In children, however the case is different Its appearance furnishes very strong evidence in favor of some form of meningitis although it undoubtedly is encountered occasionally in other brain diseases It was present in 63 per cent of our cases of meningitis in children As regards the undulatory type of irregularities it must be said that this form of breathing is seen too frequently in various other severe diseases to render it of much value in the diagnosis of meningitis It is entitled to consideration only when present in some of its more pronounced forms and when associated with other symptoms of meningitis

In a patient suspected of meningitis the continued absence of irregularities of respiration if they have been sought for carefully and persistently, should make one cautious in accepting that diagnosis There are few instances of that disease which do not at some time show distinct evidences of such disturbance

SUMMARY

Irregularities in the respiratory rhythm were observed at some time in the course of the disease in all of the thirty-two cases of tuberculous meningitis, and in all but two of the eleven non-tuberculous cases These irregularities often appear early in the disease and in most cases are to be seen much of the time throughout the course of the illness Toward the end of life, however, the breathing is apt to become very rapid and quite regular The respiratory irregularities could be grouped into three fairly distinct classes, although intermediate forms were often met with The three classes are (a) The type of Cheyne-Stokes (b) Biot's meningitic type, and (c) an undulatory type

Cheyne-Stokes breathing was seen in 53 per cent of all the cases and in 63 per cent of the cases in children It was of more frequent occurrence among the cases of tuberculous meningitis than among the non-tuberculous ones

As observed in children, this type of respiration presents certain features which distinguish it from the form seen in adults These peculiarities, we believe, are related to the age of the patient rather than to the nature of the disease, in other words it is an infantile type of Cheyne-Stokes rather than a meningitic type The form of periodic breathing described by West and called "grouped respirations," seems to be identical with the more extreme examples of the infantile type of Cheyne-Stokes

Biot's breathing was observed in 27 per cent of the forty-three cases Its incidence among the adults and among the non-tuberculous cases was considerably greater than among the children and the tuberculous cases It was seen at all stages of the disease and occasionally was met in cases which at other times showed the Cheyne-Stokes type

The third group of respiratory irregularities, designated as the undulatory type, showed no apneic pauses, but was characterized by undulatory and more or less rhythmical variations in the rhythm and force of the respirations and in the tonicity of the respiratory muscles This form of respiratory disturbance was seen at some time in the course of almost every case

No distinct relationship could be detected between the presence of respiratory irregularities and irregularities in the pulse, nor were the respiratory arhythmias dependent on any special mental state such as stupor or coma The diagnostic significance of respiratory irregularities varies with the type Biot's breathing, when it occurs, may be regarded as almost pathognomonic of meningitis The Cheyne-Stokes type has little or no diagnostic value in adults, but in children it is seen much more frequently in meningitis than in any other condition, and, if associated with other suggestive symptoms, should always arouse grave suspicion of that disease The undulatory type of irregularities is found too often in other diseases to be of much value in the diagnosis of meningitis

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A STUDY OF STREPTOCOCCUS ANTIBODIES IN SCARLET FEVER WITH SPECIAL REFERENCE TO COMPLEMENT FIXATION REACTIONS

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Owing to the fact that scarlet fever has long been noted a contagious disease, it is not surprising that early and persistent attempts were made to discover its exact cause Many years before the development of bacteriology, investigators believed that a specific contagium was present and searched for it, mainly in the blood with then crude magnifying lenses

In 1869 Hallier considered the micrococcus which he claims to have seen in the blood corpuscles of scarlet fever patients to be the cause From then until 1884 when Loeffler isolated a streptococcus from the throat of a scarlet fever patient, various cocci bacilli and "bodies" were discovered in the skin, blood and urine brought forward as the solution of the problem, received no confirmation, and dropped into oblivion

In 1885 Powers noted the presence of scarlet fever among the consumers of milk from the Hendon farm, England The udders of the cows were found ulcerated Klein delegated to make bacteriological examinations of the cows, isolated streptococci Later he secured streptococci from scarlet fever patients and considered these organisms analogous to those secured from the cows Certain individual characteristics were ascribed to these streptococci, and Klein believed a streptococcus to be the specific organism of scarlet fever

Since then Fiessinger, Dowson, Berge Limone, Baginsky and Sommerfeld have either positively or tentatively regarded streptococci as the cause of the disease Gordon, Pearce, Hektoen, Schamberg, Gildersleeve, Bergey and I have noted the close relation of streptococci to scarlet fever In 1889 Class of Chicago described a large Gram-negative diplococcus found in scarlet fever cases and which he considered the exact cause His work has not received uniform confirmation, although it is certainly true that his diplococcus occurs in a large number of scarlet fever patients

In 1887 Pfeiffer described protozoa-like bodies in the blood of scarlet fever patients, and in 1904 interest in this phase of the subject was renewed by the researches of Mallory, who described certain bodies,

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*From the Laboratory of the Philadelphia Hospital for Contagious Diseases

*Read before the joint meeting of the New England, New York and Philadelphia Pediatric Societies, New York, Nov 9, 1911

Cyclastei scai latinalis, which he believed might be the cause of the disease, in the skin of scailet fevei patients

The latest contiibution to the bacteiiology of scarlet fever was made by Vipond,[1] who desciibes the specific oiganism of scailet fevei, secuied from the enlarged lymphatic glands, as being a iapidly giowing, spore-forming, acid-pioducing bacillus Bouillon cultuies of this oiganism aie claimed to have pioduced the disease in monkeys and iabbits In my own[2] bacteiiological investigation of the glands in twenty-six cases of scailet fevei, I failed to find in any case any organism iesembling those described by Vipond In nine of these cases stieptococci weie found

As will be noted, stieptococci have ieceived most attention in ieseaiches in scailet fever Piactically all the work was conceined in establishing the fiequency with which stieptococci occuiied in this infection and whethei oi not they possessed such moiphological and biological chaiacteis as would enable one to identify them fiom the bioad class of stieptococci and theieby establish theii exact ielation to scailet fever Since 1905 inteiest has been ienewed in this subject by the repoits of Russian physicians conceining the efficacy of piophylactic injections of stieptococcus bacteiins (vaccines) in scailet fevei Gabiickevsky[3] piobably the fiist to advocate the piactice of stieptococcus immunization, while not expiessing himself definitely as believing a stieptococcus to be the cause of scarlet fevei, ceitainly believes that it beais a veiy close etiological ielation to the disease He piepaies his vaccine fiom cultuies of stieptococci secured at autopsy of scailet fevei patients and kills the emulsion by heating foi one hour at 60 C So far as I am able to asceitain the method has not been in piactice outside of Russia If stieptococcic immunization does absolutely pievent scailet fevei, then a stieptococcus not only beais a close relation to the disease but may be consideied the specific cause

Confident that scailet fevei stieptococci do not possess any specific cultuial oi moiphological chaiacteiistics, I began to study the antibodies of a numbei of diffeient cultuies fiom vaiious souices with two main objects in view

1 To deteimine moie accuiately, if possible, by such study the ielation of stieptococci to scailet fevei than is possible by moiphological and biological studies alone

2 To deteimine if the method of stieptococcus immunization as piacticed in Russia can be supported by laboiatoiy investigation

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1 Vipond, A E Scailet Fevei Preliminaiy Note of its Specific Micioorganism, Aich Pediat, 1911, xxviii, No 7, p 564

2 Kolmei, J A A Note on the Bacteiiological Examination of Lymphatic Glands in Scailet Fevei, Am Joui Dis Child 1911, ii 329

3 Gabiickevsky Stieptococcic Vaccines and Theii Application in Scarlatina Russk Viach, 1905, iv, 941

ORGANISMS AND IMMUNE SERUMS

In all of the following experiments the same cultures and immune serums were used. Accordingly reference will be made to culture and serums by number only. For instance, Antigen 1 means that it was made of Streptococcus Culture 1, and Immune Serum 1 means that it was produced by injections of Streptococcus Culture 1 and so on through opsonins and agglutinins.

No. 1.—Streptococci secured from scarlet fever patients. A horse was immunized (Immune Serum 1) by three injections of streptococci killed by exposing to 60 C. for one hour, the next two injections were of attenuated organisms after exposure to 50 C. for thirty minutes and the last injection preceding bleeding was of living cultures. All injections were subcutaneous.

No. 2.—A streptococcus secured by blood-culture from a case of scarlet fever. A rabbit was immunized (Immune Serum 2) by six intravenous injections, at intervals of a week, of organisms exposed to 60 C. for one hour.

No. 3.—A streptococcus from a case of septicemia, obtained from Dr. A. P. Hitchens. A rabbit was immunized (Immune Serum 3) by six intravenous injections of organisms exposed to 60 C. for one hour.

No. 4.—A streptococcus, isolated by Fillin from a case of septicemia and obtained from the American Museum of Natural History, New York. A rabbit was immunized (Immune Serum 4) by six intravenous injections of organisms exposed to 60 C. for one hour.

No. 5.—A streptococcus isolated from a non-scarlatinal tonsillitis. A rabbit (Immune Serum 5) was immunized by six intravenous injections of organisms exposed to 60 C. for one hour.

The injections were given every seven days and the serum tested from time to time by bleeding from the ear. At the end of seven weeks the rabbits were killed and serum stored in sterile tubes in the refrigerator without the addition of preservatives. Normal horse serum was secured from two healthy animals and normal rabbit serum from six large healthy rabbits.

COMPLEMENT FIXATION REACTIONS

It is reasonable to suppose that immune bodies exist in the blood of persons having recovered from scarlet fever, as this disease is specifically infectious, runs a definite course and confers a specific immunity in the great majority of cases.

In 1904 Besredka[4] applied complement fixation reactions to the study of horses immunized with streptococci and found that the various serums produced complement fixation only with the strain of streptococci used

4. Besredka: Le sérum antistreptococcique et son mode d'action, Ann. de l'Inst. Pasteur, 1904, xviii, 363.

in producing them He concluded that we have in the fixation reaction a means of studying and differentiating streptococci Fresh emulsions of living organisms were used as antigens In the same year Besredka and Dopter[5] applied the reaction to the study of scarlet fever but without positive results Three years later Foix and Mallein[6] applied the reaction to the study of twelve cases of scarlet fever and found positive results in ten Nine controls, including serums from four cases of erysipelas and one of puerperal sepsis, yielded negative results Uppenheim[7] tried complement fixation reactions with two strains of streptococci furnished by Paltauf, with Moser's antistreptococcus serum The results were negative, and while he does not give any details of his technic, he concludes that Moser's serum did not contain streptococcus antibodies Castex,[8] using a fresh emulsion of apparently one strain of streptococcus, applied the reaction in the study of four cases of erysipelas, five cases of scarlet fever and a case each of streptococcus abscess, puerperal fever, pleurisy and arthritis, securing positive reactions in all but three cases of scarlet fever He expresses his belief in the unity of the streptococcus Sommerfeld,[9] using a fresh emulsion of streptococci as antigen, found no fixation in scarlet fever Livierato studied eighteen cases of scarlet fever and found all positive with an antigen of scarlet fever streptococci and negative with antigens of staphylococci, diplococci, *Bacillus typhosus,* etc Swift and Thro,[10] after studying three strains of streptococci, three strains of diplococci and one of *Staphylococcus aureus,* found that immune bodies specific for different strains of streptococci, can be demonstrated by means of the complement fixation test To these investigators is also due great credit for working out a satisfactory method of preparing bacterial antigens

Since it is apparently possible for one not only to detect streptococcus antibodies in serum, but also to differentiate streptococci by complement fixation reactions, it was considered advisable to study scarlet fever serums and determine in what percentage of cases streptococcus antibodies could be found Although it is possible to find streptococci in a large per-

5 Besredka and Dopter Du rôle des streptocoques au cours de la Scarlatine, Ann de l'Inst Pasteur, 1904, xviii, 373

6 Foix, C, and Mallein, E La réaction de Bordet et Gengou vis à vis du streptocoque dans la scarlatine, Presse méd, 1907, xv, 777

7 Uppenheim, A Ueber Komplementbindung bei Scharlach, Munchen med Wchnschr, 1909, lvi, 2471

8 Castex, M R Recherches cliniques sur la présence d'anticorps streptococcies dans les serums des malades atteints de streptococcies diverses, Presse méd, 1909, xvii, 324

9 Sommerfeld, P Ueber Komplementablenkung bei Scharlach Arch f Kinderh, 1909, l, 38

10 Swift, H F, and Thro W C A study of Streptococci with the Complement Fixation and Conglutination Reactions, The Archives Int Med 1911 vii 24

centage of scarlet fever cases, yet streptococci may be found in from 60 to 70 per cent of healthy throats (Ruediger) and therefore this organism may be perfectly harmless in a certain proportion of scarlet fever patients This part of the study may be considered under two heads

1 To apply the principles of complement fixation in the differentiation of streptococci after experimental immunization of animals

2 To study scarlet fever serums with suitable antigens in order to detect streptococcus antibodies and ascertain if these antibodies are specific

TECHNIC

1 Complement—Fresh guinea-pig serum titrated for exact strength One unit was used in each tube

2 Hemolysin—The serums of rabbits immunized to sheep corpuscles The hemolytic unit was determined each time before setting up the tests and was so diluted that 1 c c of the dilution contained two units

3 Corpuscle Suspension—Defibrinated sheep's blood washed three times with 0 85 per cent salt solution and made up to a 5 per cent suspension with saline 1 c c of this was used in each tube

4 Immune or Normal Rabbit Serum—The serum was heated to 55 C for twenty-five minutes and used in increasing amounts

5 Antigens—The preparation of these is most important Fresh emulsions are usually so highly anticomplementary in comparison to their antigenic value as to be useless I have used practically the same method devised by Swift and Thro The secret consists in drying the organisms at the lowest possible temperature and preferably in a vacuum over calcium chlorid or sulphuric acid

The steps in the procedure were as follows

1 Cultures were grown on slanted gelatin agar in large bottles for four days

2 Growths were washed off carefully with 0 85 per cent saline solution and examined to make sure that the culture was pure

3 The emulsion was strained, in case fragments of the media came away

4 The emulsions were thrown down in a high speed electric centrifuge

5 The bacteria in the bottom of the centrifuge tube were dried in a cold room over calcium chlorid

6 Tubes were plugged and paraffined and put away in the refrigerator until all serums were in readiness for the fixation tests

7 The dried organisms were ground in a mortar with 0 85 per cent saline solution containing 0 5 per cent phenol in the proportion of about 0 05 gm to 1 c c of the saline

8 The emulsions were shaken with glass beads for forty-eight hours and then centrifuged to clearness. The supernatant fluid was stored in stained glass bottles in the refrigerator. Such antigens were found to keep about one week The dried organisms may be kept for months and the antigen made up as needed.

Complement, antigen and serum were mixed and the total quantity brought up to 5 c c by the addition of 0 85 per cent. salt solution Tubes were incubated at 37 C for one hour and then two units of hemolysin and 1 c c of the 5 per cent suspension of corpuscles added. Tubes were incubated for two hours and then placed in the refrigerator for twenty-three hours, when results were noted.

The exact anticomplementary and fixing strengths of the antigens were determined in the manner shown in Table 1.

TABLE 1 —DETERMINATION OF ANTICOMPLEMENTARY AND FIXING POWER OF THE DIFFERENT STREPTOCOCCUS ANTIGENS

Amt of Serum, c c	Amt of Antigen, c c	Antigen 1	Antigen 2	Antigen 3	Antigen 4	Antigen 5
ANTICOMPLEMENTARY POWER—						
	06	C H*	C H	C H	C H	C H
	08	C H	C H	C H	C H	C H
	1	C H	C H	C H	C H	C H
	15	C H	C H	C H	C H	C H
	18	C H	C H	S I H	C H	S I H
	2	S I H	S I H	M I H	S I H	M I H
	3	M I H	M I H	C I H	M I H	C I H
FIXING POWER—						
Immune Serum						
2	06	S I H	C H	S I H	C H	C H
2	08	M I H	S I H	S I H	C H	S I H
2	09	I H	M I H	M I H	C H	M I H
2	1	I H	M I H	M I H	S I H	I H
2	12	I H	I H	I H	S I H	I H
2	15	I H	I H	I H	M I H	I H
2	2	I H	I H	I H	M I H	I H
Normal Serum						
2	06	C H	C H	C H	C H	C H
2	08	C H	C H	C H	C H	C H
2	09	C H	C H	C H	C H	C H
2	1	C H	C H	C H	C H	C H
2	12	C H	C H	C H	C H	C H
2	15	C H	C H	S I H	C H	C H
2	2	S I H	S I H	I H	S I H	M I H

*C H indicates complete hemolysis, S I H slight inhibition of hemolysis, M I H marked inhibition of hemolysis, I H complete inhibition of hemolysis

It will be noted that the immune body content was fairly pronounced in all serums except from Rabbit 4, in which it was rather low Having determined the anticomplementary and antigenic units of each antigen and the amount of antibody in each immune serum we were ready for the most important step of all, to determine if the antibody is specific for the streptococcus used in producing it To determine this, it was necessary

to try out each immune serum with each antigen separately and note the results, as shown in Tables 2, 3, 4, 5 and 6

TABLE 2.—FIXING POWER OF SERUM 1

Amt of Serum, c c	Antigen c c	Streptococcus 1	Streptococcus 2	Streptococcus 3	Streptococcus 4	Streptococcus 5
05	0 1	S I H	S I H	C H	C H	C H
08	0 1	M I H	S I H	C H	C H	C H
0 1	0 1	I H	M I H	C H	C H	S I H
0 15	0 1	I H	I H	S I H	S I H	S I H
0 2	0 1	I H	I H	S I H	M I H	M I H

It will be noted (Table 2) that complement fixation is most marked with the scarlet fever streptococcus antigens 1 and 2

TABLE 3.—FIXING POWER OF SERUM 2

Amt of Serum, c c	Antigen c c	Streptococcus 1	Streptococcus 2	Streptococcus 3	Streptococcus 4	Streptococcus 5
05	0 1	S I H	S I H	C H	C H	C H
08	0 1	S I H	S I H	C H	C H	C H
0 1	0 1	M I H	M I H	C H	C H	C H
0 15	0 1	M I H	M I H	S I H	C H	S I H
0 2	0 1	I H	I H	M I H	S I H	S I H

Table 3 shows again that complement fixation is most marked with the scarlet fever streptococcus cultures It is important to note in these tables that the tendency to specificity of serums and antigens is noted only in the higher dilutions of serum

TABLE 4.—FIXING POWER OF SERUM 3

Amt of Serum, c c	Antigen c c	Streptococcus 1	Streptococcus 2	Streptococcus 3	Streptococcus 4	Streptococcus 5
05	0 1	S I H	S I H	S I H	C H	C H
08	0 1	M I H	M I H	M I H	C H	C H
0 11	0 1	I H	I H	I H	S I H	C H
0 15	0 1	I H	I H	I H	M I H	S I H
0 2	0 1	I H	I H	I H	I H	M I H

It will be noted that the fixing power of Serum 3 (Table 4) with its own antigen (3) was no greater than with Antigens 1 and 2 In this respect it did not show any specific action although with Antigens 4 and 5 fixation resulted only with lower dilution of serum

TABLE 5.—FIXING POWER OF SERUM 4

Amt of Serum, c c	Antigen c c	Streptococcus 1	Streptococcus 2	Streptococcus 3	Streptococcus 4	Streptococcus 5
05	0 1	C H	C H	C H	C H	C H
08	0 1	C H	C H	C H	C H	C H
0 1	0 1	C H	C H	C H	C H	C H
0 15	0 1	C H	C H	C H	S I H	C H
0 2	0 1	S I H	S I H	S I H	M I H	C H

The antibody content of Serum 4 (Table 5) was quite low, so that fixation occurred only in low dilution It proved, however, to be slightly specific in nature

TABLE 6.—FIXING POWER OF SERUM 5

Amt of Serum, c c	Antigen c c	Strepto-coccus 1	Strepto-coccus 2	Strepto-coccus 3	Strepto-coccus 4	Strepto-coccus 5
05	0 1	C H	C H	C H	C H	C H
08	0 1	C H	C H	C H	C H	S I H
0 1	0 1	S I H	S I H	C H	C H	M I H
0 15	0 1	S I H	S I H	S I H	C H	I H
0 2	0 1	M I H	M I H	S I H	S I H	I H

The immune body in Serum 5 (Table 6) showed its specific character in the higher dilutions of serum

Of interest here is the complement fixation reactions with polyvalent streptococcus serum (Table 7) sent me by Dr A P Hitchens, director of the Mulford Biological Laboratories The horse, No 349, had been immunized by subcutaneous injections of streptococci from various sources, including scarlet fever streptococci which I sent to Dr Hitchens

TABLE 7.—FIXING POWER OF POLYVALENT SERUM

Amt of Serum, c c	Antigen c c	Strepto-coccus 1	Strepto-coccus 2	Strepto-coccus 3	Strepto-coccus 4	Strepto-coccus 5
05	0 1	C H	C H	S I H	C H	M I H
08	0 1	C H	C H	I H	C H	I H
0 1	0 1	S I H	S I H	I H	C H	I H
0 15	0 1	S I H	S I H	I H	S I H	I H
0 2	0 1	S I H	S I H	I H	M I H	I H

It will be noted in Table 7 that fixation is best marked with Streptococcus 5, isolated from a case of streptococcic tonsillitis, then with Streptococcus 3, a culture sent me by Dr Hitchens The serum also contained antibodies for scarlet fever streptococci as demonstrated by the reactions with 1 and 2 This would tend to show that each streptococcus produced its own antibody.

COMPLEMENT FIXATION WITH SCARLET FEVER SERUMS

Serums from 107 patients with scarlet fever were examined and these cases may be analyzed as follows

Scarlet fever simplex	104 cases
Scarlet fever malignant	3 cases

During the first week or ten days of scarlet fever, the rash is present and begins to fade, during the second week desquamation is usually well marked and is completed by the sixth or seventh week Serum from these patients was secured at the following periods of the disease·

Week of Disease	Cases	Week of Disease	Cases
First	38	Fourth to fifth	6
Second	31	Fifth to sixth	4
Second to third	12	Sixth to eighth	3
Third to fourth	13		

All of these serums were examined with an antigen of Streptococcus 1 The technic was the same as that already given, only emphasis is again laid on the importance of accurate titration of complement and amboceptor

Results Serums from twelve cases, or 11 2 per cent, yielded positive reactions as follows

Week of Disease	No Positive	Week of Disease	No Positive
First	4	Fourth	2
Second	2	Sixth to seventh	2
Third	2		

Eight of these positive serums yielded negative reactions with the regular Wassermann system of luetic liver antigen Six of the above positive serums were tried out with the other three streptococcus antigens, yielding negative results with the higher dilutions of serum

Of interest here is the work of Much and Eichelberg,[11] who applied the complement fixation reaction to scarlet fever serums with antigen of luetic liver, not with the purpose of studying the hypothetical immune bodies of scarlet fever, but to ascertain if the antigen used in the diagnosis of syphilis would unite with something in the serum, deviate complement, and thus render the serodiagnosis of syphilis less reliable Their report stimulated considerable work with widely different results In June, 1911, I reported[12] the result of the study with the Wassermann and Noguchi systems of 250 cases of scarlet fever in all stages of the disease with uniformly negative results A large number of these same serums were used in this streptococcus work

CONCLUSIONS

I believe that the following deductions are correct

1 A streptococcus produces a specific antibody up to a certain limit The specific nature of these antibodies is seen by complement fixation reactions in high dilutions between a streptococcus immune serum and its antigen With low dilutions, however, the specific nature of the antibody is not brought out

11 Much and Eichelberg Die Komplementbindung mit wasserigen Luesextrakt bei nichtsyphilitischen Krankheiten, Med klin, 1908, iv, 671

12 Kolmer, J A Complement Deviation in Scarlet Fever with Comparative Studies of the Wassermann and Noguchi Systems, Jour Exper Med, 1911, xiv, 235

2 Not only do scarlet fever streptococci tend to produce their own specific immune serum, but likewise streptococci causing septicemia and those causing non-scarlatinal angina, etc, tend to produce their own immune serums Therefore it does not seem any more justifiable to claim a specific streptococcus for scarlet fever than it does to make such a claim for a specific streptococcus causing septicemia and other conditions

3 Finding but 11 2 per cent positive reactions in scarlet fever tends to show that streptococcus infection in scarlet fever severe enough to produce immune bodies is not so common as is generally believed One of the three toxic or malignant cases yielded a positive reaction These severe cases are frequently due to an overwhelming effect of the true scarlet fever virus, whatever that may be, without secondary streptococcus infection

OPSONINS

Since it has been practically proved that a streptococcus is not the cause of scarlet fever it is difficult to understand how immunization with streptococci can prevent that disease We can understand, however, that such immunization may be of value in preventing or mitigating secondary streptococcic infections which are present in at least 11 per cent of scarlet fever patients and responsible for severe primary lesions and complications Likewise, it is probable that such protection would result by an increase in opsonins against streptococci The question of method, however, relative to production of opsonin is very important, and accordingly this study had two main objects in view

1 To ascertain if the streptococco-opsonic index can be raised by the injection of heat-killed streptococci Since the Russian physicians advise two or three doses of vaccine as a prophylactic, my special object was to determine if this number of injections was sufficient to raise the opsonic index

2 To ascertain whether the opsonins produced by the different strains of streptococci were specific in nature

The opsonic index of normal serum is low for streptococci from all sources Bordet, in a study of antistreptococcic serum, says that he believes that streptococci exert a negative chemotactic influence and that the administration of the serum removes this influence and stimulates phagocytosis Banks[13] and Tunnicliff[14] have shown that early in scarlet fever the streptococco-opsonic index is usually below normal, that it rises rather sharply with the decline of fever and amelioration of symptoms and then slowly falls to normal during convalescence If the injection of

13 Banks Variations in Scarlet Fever of the Opsonic Power of Streptococci, Jour Path and Bacteriol 1907 xii 113

14 Tunnicliff R The Streptococco Opsonic Index in Scarlatina, Jour Infect Dis 1907 iv 304

streptococcus vaccine can prevent streptococcus infection, then it seems reasonable to suppose that it does so by increasing the quantity of opsonins against streptococci and that this could be demonstrated experimentally Simonds[15] was able to raise the streptococco-opsonic index of rabbits by injecting heat-killed streptococci. Weaver and Tunnicliff were not able to do this with heat-killed organisms but were successful after injecting emulsions killed in 25 per cent solution of galactose In the Russian method of preventive inoculation the vaccines are killed by heat and if it is true that vaccines do not increase opsonins it is difficult to understand how protection is brought about

TECHNIC AND RESULTS

The same cultures and immune serums were used as in the complement fixation tests Cultures showing a tendency to grow in the conglomerate masses in bouillon were trained to grow diffusely by daily subcultures in glucose + 0 5 bouillon The emulsions were thoroughly broken up with glass beads prior to use in opsonin work

The four rabbits were bled from the ear one week after the third injection of streptococci and the opsonic indices shown in Table 8 obtained

TABLE 8.—OPSONIC INDICES AFTER THREE INJECTIONS OF STREPTOCOCCI

Immune Serum	Streptococcus 2	Streptococcus 3	Streptococcus 4	Streptococcus 5
Rabbit 2	0 9	0 6	0 6	0 7
Rabbit 3	0 5	1 0	0 6	0 8
Rabbit 4	0 2	0 3	1 1	0 3
Rabbit 5	0 65	0 6	0 5	0 9

It will be noticed by Table 8 that the quantity of opsonin is slightly raised in 3 and 4 The next table (Table 9) is composed of the streptococco-opsonic indices after six injections, the horse having been bled freely from the jugular vein and the rabbits killed These examinations were made within thirty-six hours after bleeding and repeated at the end of seventy-two hours

TABLE 9.—OPSONIC INDICES AFTER SIX INJECTIONS OF STREPTOCOCCI

Immune Serum	Streptococcus 1	Streptococcus 2	Streptococcus 3	Streptococcus 4	Streptococcus 5
Horse Serum 1	3 2	3 2	1 1	1 0	1 1
Rabbit 2	1 2	1 2	0 6	0 8	0 9
Rabbit 3	0 6	0 6	1 6	0 8	0 9
Rabbit 4	0 2	0 2	0 37	1 4	0 32
Rabbit 5	0 8	0 8	0 85	0 7	1 7
Polyvalent Serum	2 8	2 8	3 3	4 1	3 6

It will be noted (Table 9) that the horse serum contains the largest quantity of opsonin This serum also gave beautiful complement fixation

15 Simonds, J P The Effect of the Injection of Killed Streptococci on the Streptococco Opsonic Index of Normal Rabbits, Jour Infect Dis, 1907, iv, 595

reactions and has proved distinctly curative in severe cases of scarlet fever treated in the wards of the Philadelphia Hospital for Contagious Diseases The quantity of opsonin has been increased in all animals by the additional three doses of streptococci The polyvalent serum, the same as used in the complement fixation tests, shows a high opsonin content for all strains of streptococci, especially the non-scarlatinal strains.

CONCLUSIONS

1 It is possible to raise the streptococco-opsonic index by the injection of organisms killed by an exposure to 60 C for one hour This increase is very slight with three or less administrations and becomes apparent only after a relatively large number of injections

2 The increase in the quantity of opsonin after three injections is so slight as to make the likelihood of establishing an immunity against streptococcic infection very dubious

3 The opsonins were more or less specific toward the strains used in the process of immunization

AGGLUTININS

Streptococci stimulate the production of agglutinins but the quantity produced varies within wide limits Investigation tends to show that such agglutinins are not specific in character and for this reason agglutination reactions are of little value in the study of streptococcus infections The reports of investigations, however, are far from agreeing on this point and since I worked on this problem with much interest I thought it would not be amiss to record my results

The first studies in agglutination of streptococci by immune serums were made, according to Weaver,[16] by Van de Velde, who found anti-streptococcus serum to have weak agglutinating power over homologous streptococci but none over other strains Moser and von Pirquet, Meyer, Wlassjenski and Salve found agglutinins present in immune serums and considered them more or less specific in nature Krauss and Aronson secured negative results The work of the latter needs special mention because of its more thorough character He immunized horses with cultures of streptococci from scarlet fever, rheumatism and otitis media and after careful agglutination tests with the immune serums insists that in no case is one able to differentiate streptococci by the most careful work Weaver also made an excellent report on the agglutination of streptococci Cultures from various sources, including scarlet fever, phlegmon, puerperal sepsis, endocarditis, etc., were used Serums from various diseases were tested It was found that scarlet fever streptococci were agglutinated

16 Weaver Agglutination of Streptococci, Especially Those Cultured from Cases of Scarlatina, by Human Sera, Jour Infect Dis, 1904, 1, 91

by the serums from pneumonia, erysipelas, typhoid fever and puerperal sepsis and that agglutination between scarlet fever streptococci and scarlet fever serum is in no way specific and cannot be of any value in diagnosis

In my investigation I used the same five immune serums as were used in the complement fixation and opsonin work These serums were five and six days old when the final agglutination reactions were set up They were kept in a refrigerator without the addition of preservatives In addition to the agglutination reactions with the five immune serums, the serums of thirty-two scarlet fever patients were examined

TABLE 10.—SHOWING RESULTS OF AGGLUTINATION OF STREPTOCOCCI BY IMMUNE SERUMS

Streptococcus	Dilutions 1/10	1/15	1/20	1/25	1/30	1/40	1/100	1/140
IMMUNE SERUM 1								
1	+	+	+	+	+	+	+	—
2	+	+	+	+	+	+	+	—
3	+	+	+	+	+	—	—	—
4	+	+	+	—	—	—	—	—
5	+	+	+	+	+	—	—	—
IMMUNE SERUM 2								
1	+	+	+	—	—	—	—	—
2	+	+	+	—	—	—	—	—
3	+	+	—	—	—	—	—	—
4	+	+	+	+	—	—	—	—
5	+	+	+	—	—	—	—	—
IMMUNE SERUM 3								
1	+	+	+	—	—	—	—	—
2	+	+	+	—	—	—	—	—
3	+	+	+	+	+	—	—	—
4	+	+	—	—	—	—	—	—
5	+	+	+	—	—	—	—	—
IMMUNE SERUM 4								
1	—	—	—	—	—	—	—	
2	—	—	—	—	—	—	—	
3	+	—	—	—	—	—	—	
4	+	+	+	—	—	—	—	
5	+	—	—	—	—	—	—	
IMMUNE SERUM 5								
1	+	+	—	—	—	—	—	
2	+	+	—	—	—	—	—	
3	+	+	+	+	—	—	—	
4	+	—	—	—	—	—	—	
5	+	+	+	+	—	—	—	
POLYVALENT SERUM								
1	+	+	+	+	—	—	—	
2	+	+	+	+	—	—	—	
3	+	+	+	+	+	+	—	
4	+	+	—	—	—	—	—	
5	+	+	+	+	—	—	—	

TECHNIC AND RESULTS

Cultures of streptococci were subcultured daily in glucose bouillon + 0 5 phenolphthalein until they grew diffusely The macroscopic technic

was used throughout Dilutions from 1 to 10 up were employed The tubes were kept in the incubator at 36 C for two hours and examined with the aid of a magnifying glass Final readings were made at the end of twenty-four hours

Table 10 gives in detail the results of these agglutination tests with the various immune serums and different cultures of streptococci

Examination of Table 10 shows (1) The quantity of agglutinin produced was in most instances small in amount The highest values were found with the horse serum, a result of prolonged immunization with dead, attenuated and finally living cultures (2) The reactions were inconstant and quite variable (3) Agglutinins for streptococci are not specific and hence of no value in the differentiation of streptococci

STREPTOCOCCUS AGGLUTININS IN SCARLET FEVER

Serums from the thirty-two patients examined may be classified as follows·

Scarlet fever simplex	31 cases
Scarlet fever malignant	1 case

These cases included all stages of the disease

Results Agglutination of scarlet fever streptococci occurred with four serums in dilutions up to 1-to-40 All of the remaining serums yielded absolutely negative results The four positive serums also agglutinated the other streptococci, but in lower and various dilutions In no case was a high degree of agglutination demonstrable

CONCLUSIONS

1 Streptococcus agglutinins are produced slowly by experimental immunization and the quantity is quite variable

2 These agglutinins are apparently non-specific in character and of no value in differentiating streptococci

3 They were demonstrated in 12 5 per cent of scarlet fever patients but only in comparatively low dilutions of serum

4 There was no relation between agglutination and complement fixation antibodies or between agglutinins and opsonins

THE RELATION OF STREPTOCOCCI TO SCARLET FEVER

A great deal has been written under this heading In the first place I agree with those who claim that streptococci found in scarlet fever patients, whether in the throat, in suppurative lesions, or in the blood, cannot be differentiated from streptococci found normally in the throat or in septic conditions by morphological or cultural characteristics Frequently cultures from scarlet fever cases are apparently different, but these differences have been temporary and easily broken up While com-

plement fixation tests have shown a specific antibody for scarlet fever streptococci, this is true only in high dilutions of serum And further, the same specific relation is readily demonstrated between streptococci causing septicemia and streptococci causing non-scarlatinal sore throat, etc, and their immune seriums Hence, if we are to claim a specific streptococcus for scarlet fever a similar claim may be made for every other streptococcus infection and thus to claim a specific streptococcus for endocarditis and another for puerperal sepsis, etc., seems to be out of the question It is true that streptococci are found in a goodly percentage of scarlet fever cases We are confident, however, that many so-called streptococcus anginas would be found on closer examination to be pneumococcic My percentage of streptococcus blood infections in scarlet fever is somewhat lower than that obtained by others One fact is certain not all severe, septic and fatal cases of scarlet fever are due to streptococci Antistreptococcus serum, the same horse serum (Serum 1) as used in these experiments, has given good results in certain instances Patients extremely sick with the true toxemia of scarlet fever are not benefited by it at all Opsonins have been found somewhat specific for the particular culture responsible for their formation but I am not yet prepared to conclude from this that a certain strain of streptococcus causes this condition and another that condition I believe that the true scarlet fever poison lowers the resistance of the patient to streptococcus infection and this is substantiated by noting the low streptococco-opsonic indices during the first week of scarlet fever How this is brought about is impossible as yet to explain A similar relation may be noted by the tendency of the diphtheria patient to contract scarlet fever We believe that the streptococcus found in scarlet fever belongs to the general class of streptococci and is modified in some way during the course of the infection so as to give it a somewhat specific antibody and occasionally temporary cultural characteristics The same is true of streptococci causing septicemia and simple sore throat How these changes are brought about constitutes an interesting field for further investigation

STREPTOCOCCUS IMMUNIZATION

The reports of Russian physicians concerning the efficacy of injections of streptococcus vaccine as a preventive of scarlet fever are on the whole quite convincing But the disease is so protean in character, is disseminated so frequently in such an inexplicable and confusing manner, so little is really understood concerning the infection, that one must review these enthusiastic reports with healthy skepticism I immunized 350 persons[17] according to the Russian method and while that number is far

17 Kolmer, J A The Relation of Streptococci to Scarlet Fever with Active Immunization by Means of Streptococcus Bacterins, Pennsylvania Med Jour, 1912, xv, No 5

too small to base an opinion on, yet it was observed that the method was without apparent value. Since experimental work does not, in my opinion, establish the identity of a specific streptococcus in scarlet fever, and from the fact that streptococci are found only in a proportion of scarlet fever cases and in many of these is apparently harmless, and since experimental work does not show an increase in opsonin after at least three injections of streptococcus vaccine sufficient to establish a good degree of immunity, I do not believe that streptococcus immunization prevents scarlet fever, although it is possible that it may prevent or mitigate the severity of secondary streptococcus infections

Second and Luzerne Streets

OSSEO-ALBUMOID AS A POSSIBLE PRECURSOR OF BENCE JONES PROTEIN

AN EXPERIMENTAL STUDY*

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1 INTRODUCTION

This study is a continuation of the preliminary work by Ottenberg and Gies,[1] who found in this laboratory that crude elastose after its subcutaneous or intraperitoneal injection can readily be detected in the urine by the heat precipitation test Since the Bence Jones protein has various properties in common with elastoses, Ottenberg and Gies suggested that osseo-albumoid (bone elastin?) might be the forerunner of the Bence Jones protein which appears in the urine of people with multiple myeloma of the bones

The basis of the experimental work described in this paper is the assumption that osseo-albumoid of the bone might be so modified by enzymes in the cells of myelomatous growths as to give rise to substances having the properties of Bence Jones protein

2 EXPERIMENTS

At the outset of this study it was necessary to ascertain whether osseo-albumoid is digestible, i e, whether proteases convert it into familiar types of hydration products Further, it was necessary to determine whether any osseo-albumoses that might thus be produced would behave like elastoses when their aqueous solutions are heated In all of these experiments the osseo-albumoid employed was made by the Hawk and Gies method [2] Some of the preparations of osseo-albumoid, as well as an abundant supply of ossein, which had been preserved by Gies, were made available for this work

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*A preliminary account of this investigation was published in Proc Am Soc Biol Chem, 1910, i, 227, Jour Biol Chem, 1910, vii, 14 A review of the history of Bence Jones protein was published by the author in the Biochem Bull, 1911, i, 161

1 Ottenberg and Gies Proc Soc Exper Biol and Med, 1907, iv, 161

2 Hawk and Gies Am Jour Physiol, 1902, vii, 340, also Gies and collaborators Biochem Researches, 1903, i, 181 (Reprint 6)

A ON THE PREPARATION OF DIGESTIVE PRODUCTS OF OSSEO-ALBUMOID

Tryptic Digestion

I A small quantity of osseo-albumoid, which had been made in a preliminary way,[3] was subjected to the action of a strong, alkaline tryptic solution for twenty-four hours at 40 C The true osseo-albumoid in the preparation was completely digested by that time Proteoses were formed A small amount of admixed collagen remained undigested The whole of this collaginous residue was readily converted into gelatin

II After five hours' digestion of fresh osseo-albumoid[4] in 80 c c of 0 25 per cent sodium carbonate containing 0 5 gm of trypsin (Merck), the mixture was filtered and the filtrate saturated with ammonium sulphate at the boiling temperature During the digestive process samples of the solution were withdrawn at intervals of forty-five minutes and when examined gave negative results in the heat-precipitation test

The ammonium sulphate precipitate was dissolved in water, dialyzed until free from sulphate and evaporated to dryness at 40 C on a water bath The residue after five hours' digestion was subjected to the action of a fresh trypsin solution and allowed to digest for eighteen hours longer, then treated by the process described above

III A sample of the original ossein-shavings was subjected to the influences of a very active tryptic solution but the shavings were apparently unaffected The filtrate from the unchanged bone-shavings was tested with fibrin as to its digestive power and found to be active A repetition of this experiment yielded the same negative result

Peptic Digestion

I A small quantity of osseo-albumoid was treated with 1 liter of 0 2 per cent hydrochloric acid containing 0 1 per cent of pepsin (P , D & Co 1 2,000) in an incubator at 40 C Portions of the digestive fluid were withdrawn at intervals and heated gradually to boiling Digestion was started at 2 30 p m At 5 30 p m there was still a small amount of material undigested and no precipitate came down on heating portions of the digestive fluid withdrawn at intervals of one-half hour during the digestion

The undigested material was filtered off and the boiling filtrate nearly saturated with ammonium sulphate Proteoses were separated as a dark scum on the surface of the solution The precipitate dissolved readily in warm water This solution was not precipitated by heat, even after dilution The solution was speedily evaporated to dryness at 40 C and in the dry state looked like scale gelatin

3 From ossein shavings prepared in 1900 and kept dry meanwhile

4 Made from a portion of the same ossein-shavings as those used in Experiment 1

The incompletely saturated filtrate from the proteoses was treated with sufficient ammonium sulphate to effect complete saturation and a small amount of dark sticky material was precipitated, which dissolved readily in warm water but gave no turbidity on heating

II In the preparation of osseo-albumoid the last portions of admixed collagen are difficult to remove In the peptic digestion of osseo-albumoid admixed with collagen, the latter is gelatinized and then converted into gelatoses and gelatin peptones It was thought that possibly such gelatin or its hydration products might have been admixed with the osseo-albumoses obtained in the preceding experiments and that, by their presence, they might have prevented the occurrence of the elastose-like reaction on heating Consequently a portion of the osseo-albumoid employed in the preceding digestion experiment was treated from time to time with boiling water until no more collagen or gelatin could be present, as indicated by practically complete absence of protein from the washings The small quantity of osseo-albumoid that remained was filtered off, washed with water and subjected to peptic digestion in 500 c c of 0 2 per cent hydrochloric acid containing 0 25 gm of pepsin (1 4,000) and placed in an incubator at 40 C at 2 25 p m

At 2 35 p m no precipitate appeared on heating a filtered sample of the digestive fluid

At 2 50 p m *a precipitate was obtained on heating, which almost completely dissolved on further heating It reappeared on cooling and then was as voluminous as that obtained on the first application of heat*

The remainder of the peptic mixture, after digesting for two hours and ten minutes, was filtered and the hot filtrate treated with ammonium sulphate A flaky precipitate was produced before the solution was completely saturated with ammonium sulphate and at a temperature of about 65 C Most of the precipitate was soluble in water The small amount of undigested matter which was obtained after filtering was further digested To the filtrate, after the digestion of this product for three hours, was added ammonium sulphate to saturation

The substance precipitated by ammonium sulphate had the following properties

1 The reaction of its solution was acid (hydrochloric)

2 On heating this solution a precipitate was produced which dissolved on further heating and, on cooling, reappeared Heated again, the same reactions were obtained, but after a third heating of this solution, the precipitate did not entirely disappear on boiling

3 Duplication with another sample by the treatment just described (2) led to immediate precipitation on heating but boiling did not entirely clarify the mixture On cooling, however, the precipitate was more marked than before

4 A portion of the solution was neutralized Heating failed to produce a precipitate in it.

5 The same negative result (4) was obtained with the alkalized solution

6 After diluting the original solution, no precipitate was formed on heating

7 A bulky white flocculent precipitate was formed when the solution was added to alcohol (sulphates?) A solution of this precipitate gave no precipitate on heating

The elastose-like precipitation that ensued on heating the acid solution (2,3) led to the conclusion that possibly the result was due to a constituent of the pepsin Accordingly, a solution was made of pepsin in 0 2 per cent hydrochloric acid and, on heating, a faint clouding of the solution took place, but without further change on boiling or on subsequent cooling

Saturation of this peptic solution with ammonium sulphate failed to yield an appreciable precipitate

III Pure osseo-albumoid was treated with 1 liter of 0 2 per cent hydrochloric acid containing 0 5 gm of pepsin (1 . 4,000) and placed in an incubator at 35 C at 11 05 a m

At 11 45 a m most of the material had disappeared into solution Some of the liquid was withdrawn and, on adding ammonium sulphate with very little heating, a dark substance was precipitated, which proved to be insoluble in water, and was returned to the digestive mixture

At 12 m about 15 c c of the fluid were withdrawn and filtered The filtrate was saturated with ammonium sulphate in the cold A white flaky material was precipitated, which was readily soluble in water but on heating this solution no precipitate was formed

A sample of the pure pepsin-acid solution, which was used in the foregoing experiment, was saturated with ammonium sulphate A very slight amount of precipitate was formed which dissolved in water but gave no precipitate on heating

The remainder of the solution of the ammonium sulphate precipitate was dialyzed till free from sulphate and then evaporated to dryness on a water bath at 40 C The dialysate contained very little protein as was shown by the practically negative response to the biuret test

IV Osseo-albumoid was prepared as before An attempt was made to obtain a product at an earlier stage in the preparation process than that of the preceding experiment The product was fluffy as usual and had a blood-red color

This crude osseo-albumoid was subjected to the peptic conditions of the previous experiment Digestion was started at 9 45 a m

At 10 35 and 10 50 a m , heating a portion of the filtered digestive liquid failed to cause turbidity in it At 11 05 a m a portion of the

digestive fluid was withdrawn and saturated with ammonium sulphate *in the cold* A yellow sticky precipitate was formed It was completely soluble in warm water No precipitate was formed on heating this solution A portion of the solution was saturated with ammonium sulphate at the boiling temperature A precipitate was formed, which was soluble in water but gave no precipitate on heating

At 11 30 a m about one-eighth of the original bulk of material remained undigested It was filtered off and subjected to the action of a fresh pepsin-acid solution This residue did not, however, undergo digestion on further treatment with pepsin-hydrochloric acid and looked like hematin It was soluble in sodium carbonate, from which solution it could be precipitated by acidification Its solution gave the spectroscopic lines of acid hematin

The filtrate from the undigested material was saturated with ammonium sulphate *in the cold* The precipitate had a reddish color The filtrate from this precipitate was saturated with ammonium sulphate at the *boiling* temperature Each of these precipitates was dissolved in water and portions of the solution, each made neutral, acid or alkalin, were gradually heated to boiling Precipitation failed to occur in every instance After dilution of the solutions with water no precipitation occurred on heating

The remainders of the solutions of these precipitates were dialyzed free from sulphate and speedily evaporated to dryness on a water bath at 40 C The dialysates contained little or no protein, as shown by the practically negative results with the biuret test

V Osseo-albumoid was subjected to peptic digestion It was placed in an incubator at 9 15 a m and at 12 15, *one-half* of the digestive solution was removed and precipitated by saturation in the *cold* with ammonium sulphate, after careful neutralization with sodium hydroxid At the point of neutralization a voluminous precipitate was obtained which was filtered off and, on testing, was found to be easily soluble in dilute nitric acid, and to give a yellow precipitate with ammonimum molybdate but no protein reactions It was thought, therefore, that this precipitate consisted of phosphates that had not been removed by the acid treatment of the original ossein-shavings

The ammonium sulphate precipitate produced by saturation at *room* temperature was filtered off and the filtrate saturated with ammonium sulphate at the *boiling* temperature An aqueous solution of these products did not yield a heat-precipitation test

The remaining half of the digestive mixture, after eight and one-half hours' digestion, was filtered, the filtrate neutralized, the phosphates filtered off and ammonium sulphate added to saturation, as in the treatment of the first half

A considerable amount of solid substance remained at the end of the digestive treatment This was subjected to peptic digestion for twenty-four hours longer (a total of thirty-two hours) and then filtered and treated by the ammonium sulphate process described above

Each of the precipitates was dissolved in water, dialyzed till free from sulphate and speedily evaporated to dryness at 40 C

VI Fresh ox-femurs were used and osseo-albumoid was isolated from the hashed ossein-shavings as in Experiments I to IV.

A portion of the product was subjected to peptic digestion as in the previous experiments (I to IV), and after four hours' digestion, the mixture was filtered and the filtrate neutralized with sodium hydroxid The precipitated phosphates were removed by filtration and the remaining solution saturated with ammonium sulphate at the boiling temperature

The precipitate obtained by the saturation process was dissolved in water, dialyzed free from sulphate and speedily evaporated to dryness at 40 C over a water bath This product when dissolved in water did not give the heat-precipitation test The residue which remained undigested after four hours was again subjected to digestion for eighteen hours longer, and the fluid then treated by the process described above

Summary of Results of Procedure A

1 Osseo-albumoid prepared from ossein-shavings made in 1900 and kept dry, meanwhile, yielded osseo-albumoses on tryptic digestion

2 Ossein-shavings themselves were not appreciably affected by tryptic digestion

3 Osseo-albumoid made from old desiccated ossein-shavings, when subjected to peptic digestion for one-half hour, yielded a product which gave a sharp heat-precipitation test, that is, a precipitate came down on heating some of the filtered digestive mixture, which precipitate dissolved on further heating and reappeared on cooling An aqueous solution of the precipitate produced by ammonium sulphate-saturation of this digestive mixture, gave the same heat-precipitation result This result could be obtained only when the reaction of the heated solution was acid

4 The pepsin used for the digestion was not responsible for this reaction

5 After subjecting osseo-albumoid (some of the product referred to above) to peptic digestion for one one and one-half and three hours respectively, in no case did the filtered digestive mixture nor a solution of the ammonium sulphate-saturation precipitate from the digestive mixture, give a heat-precipitation test

6 Osseo-albumoid isolated from fresh ossein-shavings, after four hours of peptic digestion did not yield products giving a heat-precipitation test

7 From the above it is obvious that, with the exception of the product obtained at the end of one-half hour of peptic digestion of osseo-albumoid, none of the products gave a heat-precipitation test, thereby differing from elastoses which have properties not unlike the Bence Jones protein in some respects However, these products as obtained above, after passage through the body, might be so changed that, when excreted in the urine, they would give reactions like those of the Bence Jones protein On this theory the following experiments were tried

B SUBCUTANEOUS INJECTION OF PRODUCTS OF THE PEPTIC DIGESTION OF OSSEO-ALBUMOID

EXPERIMENT 1.—The dog in this experiment was under observation in the laboratory two days previous to the injection and during that time his urine gave no precipitate on heating, but saturation with ammonium sulphate produced a small amount of yellowish precipitate soluble in water On heating this solution, no precipitate was formed, nor did it give a reaction with picric acid or trichloracetic acid The solution gave the spectroscopic picture of urobilin The urine, however, gave a marked precipitate with potassium mercuric iodid This precipitate dissolved on further heating and reappeared on cooling The urine did not give a precipitate with picric acid or trichloracetic acid[5]

Of the substance obtained by peptic digestion of osseo albumoid (A, II, 2) 0 3895 gm was dissolved in 6 c c of 0 85 per cent sodium chlorid and injected into the loose cellular tissue of the right flank at 11 50 a m, Nov 27, 1908

Weight of the dog, 9 65 kilos, temperature of the dog, 101 2 F Amount of substance injected per kilo of dog, 0 04 gm The dog showed great lassitude for about seven hours after the injection

The urine was tested during a period of twenty-four hours after the injection, by heating and also by addition of picric and trichloracetic acids, but no precipitate came down With potassium mercuric iodid all fractions gave a marked precipitate on heating which disappeared on further heating and reappeared on cooling The fractions were obtained eight, twelve and twenty-two hours after the injection

The remainder of each fraction of urine after the above tests were made was saturated with ammonium sulphate at room temperature and the precipitate collected Fractions 2 and 3 gave small amounts of proteose-like precipitates These precipitates were dissolved in water, filtered and filtrates tested as follows

Fraction 1 did not give a precipitate on heating but with picric acid gave a precipitate which dissolved on heating and reappeared on cooling On heating

5 It was thought that the reaction with potassium-mercuric iodid might be due to the fact that the dog had a considerable amount of mucopurulent material in the inner canthus of both eyes and that this material had gotten into the urine Some of this material from the eyes was obtained, made into a solution with 0 85 per cent sodium chlorid, filtered, and on adding potassium mercuric iodid gave a faint precipitate, which did not disappear on further heating, however As the solution was comparatively concentrated, it was diluted until its content of material was equal to about the maximum proportion that could be present in the urine At this dilution a marked clouding, but no precipitate, appeared in the test with potassium-mercuric iodid The infection of the dog's eyes was removed by irrigations with boric acid, and the cage in which the dog was kept was thoroughly cleansed The urine continued to give the reaction with potassium-mercuric iodid, however, after the mucopus as a factor in its production was ruled out

Fraction 2, a cloudiness was produced which was not cleared up by continued heating nor by addition of acid nor by dilution With picric acid, the same reaction was obtained as with Fraction 1 Fraction 3 gave a marked turbidity on heating which was not clarified by continued heating, addition of acid or dilution Picric acid produced a marked precipitate, which disappeared on further heating and reappeared on cooling With potassium mercuric iodid all the fractions gave a precipitate on heating which did not clarify on continued heating

The filtrates from the precipitates obtained by saturation with ammonium sulphate at room temperature were further saturated with ammonium sulphate at the boiling temperature The precipitates were collected, dissolved in water and filtered On heating these solutions no precipitation occurred The addition of picric and trichloracetic acids was also without precipitative effects, but potassium mercuric iodid produced a precipitation on heating which disappeared on further heating and reappeared on cooling

Experiment 2.—The subject of the preceding experiment received another subcutaneous injection of 1,146 gm of osseo-albumoid (A II, 3) The amount of injected substance per kilo of the dog's body-weight was 0 1187 gm The dose was dissolved in 8 c c of 0 85 per cent sodium chlorid This was injected at 12 05 p m, Nov 28, 1908 The dog's temperature was 101 3 F No untoward symptoms developed The fractions of urine for forty-eight hours following the injection did not give any precipitate on heating, but with picric and trichloracetic acid precipitates came down which disappeared on heating and reappeared on cooling With potassium mercuric iodid all fractions gave a marked precipitate on heating which disappeared on further heating and reappeared on cooling The fractions were obtained eight, twenty-one and forty-six hours after the injection

The fractions of urine from this dog were saturated with ammonium sulphate at *room* temperature and a considerable amount of proteose-like material was collected from each This was filtered off and each filtrate saturated with ammonium sulphate at the *boiling* temperature, yielding a very small amount of precipitate The precipitates were dissolved in water, filtered and the solution tested as follows On heating in all cases a cloudiness developed which disappeared almost completely on continued heating and was restored on cooling Picric acid in all cases produced a marked precipitate which dissolved on continued heating and returned on cooling Trichloracetic acid produced a cloudiness which cleared up on heating and returned on cooling

Solutions of these precipitates of Fractions 1 and 2 were dialyzed free from sulphate and poured into alcohol A considerable amount of white, flaky precipitate came down This precipitate, after standing under alcohol for two months, became quite insoluble Sulphate was present, for the water with which the precipitate was washed gave a good reaction with barium chlorid The washings gave negative results with the Millon and the xanthoproteic tests but the insoluble precipitate gave reactions with both The washings, however, gave a biuret test, which may have been due to the presence of urobilin (Salkowski)[6] or to a small amount of the precipitate that was soluble in the water No precipitate appeared on heating the washings from the insoluble precipitate

The results of these experiments (1-2) indicate that the ammonium sulphate precipitate from the urine contained the substance injected into the dog and that this substance was rendered insoluble when precipitated by means of alcohol from its aqueous solution One of the reasons for supposing that the Bence Jones protein more nearly resembles the "pri-

6 Salkowski Berl klin Wchnschr, 1897, xxxiv, 353

many proteins" than the "secondary protein derivatives" is the fact that the albumins and globulins are rendered insoluble on standing under alcohol while the proteoses and peptones are not The result referred to above seems to indicate that the substance recovered from the urine in this experiment is closely related in its properties to the Bence Jones protein, for Simon[7] and others have shown that the Bence Jones protein is rendered insoluble in water after it has been precipitated by alcohol and allowed to stand in the reagent

Since the animal was a male, it was thought that perhaps the reaction produced in the urine by potassium mercuric iodid was due to the presence of spermatic fluid, a possibility suggested by a point to which Bence Jones[8] drew attention in his original paper He says "A similar body to Bence Jones protein may be detected in pus and in the secretion from the seminal vesicles" This reaction was obtained, however, in the urines from three bitches and ten other dogs, even after catheterization

EXPERIMENT 3.—At 11 30 a m, Dec 24, 1908, 0 7801 gm of substance (A, II, 4) dissolved in 8 c c of 0 85 per cent sodium chlorid was injected subcutaneously into a bitch The weight of the animal was 7 1 kilos The amount of substance per kilo was 0 1099 gm The dog showed no abnormal symptoms

The urine was subjected to the usual treatment The solution of the ammonium sulphate precipitate from Fraction 1 was dialyzed until free from sulphate At this point a small amount of precipitate was obtained when the solution was added to alcohol

Neither the urine nor the solutions of the ammonium sulphate precipitates gave a precipitate on heating Picric acid produced a slight precipitate which dissolved on heating and reappeared on cooling Trichloracetic acid caused an opalescence which clarified on heating and reappeared on cooling With potassium mercuric iodid a precipitate was obtained on heating which disappeared on continued heating and reappeared on cooling The fractions were obtained twenty-two, forty-five, sixty-seven and ninety-one hours after the injection

C SUBCUTANEOUS INJECTION OF PRODUCTS OF THE TRYPTIC DIGESTION OF OSSEO-ALBUMOID

Only one experiment was conducted in this particular connection The urine of the dog before injection gave no precipitate on heating nor on the addition of picric acid or trichloracetic acid

The urine was saturated with ammonium sulphate at the boiling temperature, and a dark granular precipitate obtained, which was slightly soluble in water yielding a yellow colored solution This yellow solution gave negative results in all the protein color-tests except the biuret, thus proving the presence of urobilin The solution failed to give a protein reaction with picric acid or trichloracetic acid

7 Simon Am Jour Med Sc, 1902, cxxiii, 939

8 Bence Jones Phil Tr Roy Soc Lond 1848 1 55, Proc Roy Soc Lond 1843-50, v, 673

The insoluble matter gave no protein color-tests and was soluble in acid, depositing crystals of uric acid from an acid solution on evaporation.

Of the product obtained from the digestion filtrate by saturation with ammonium sulphate (A, 1, 2), 0 9145 gm was dissolved in 11 c c of 0 85 per cent sodium chlorid This was injected subcutaneously into a dog at 10 45 a m, March 5, 1909

The weight of the dog was 7 kilos; the amount of the substance injected per kilo of the dog's weight was 0 1306 gm No unfavorable effects were noted

After the injection the urinary fractions did not give a precipitate on heating but the first fraction of urine gave a faint precipitate with picric acid and trichloracetic acid, which disappeared on heating and returned on cooling With potassium mercuric iodid a precipitate was obtained which did not dissolve completely on heating, but was restored on cooling The fractions were obtained twenty-nine, forty-eight, seventy-two and 120 hours after the injection

The fractions of urine from this dog were saturated with ammonium sulphate at the boiling temperature All the fractions, except No 1, yielded a considerable amount of proteose-like precipitate, especially Fraction 3 The precipitates produced in the fractions were dissolved in water and all fractions except No 1 gave a marked cloudiness on heating and in the case of Fraction 2, a precipitate formed which dissolved completely on continued heating and returned on cooling This fraction also gave marked precipitates with picric acid, trichloracetic acid and potassium mercuric iodid, which disappeared on heating and returned on cooling These precipitates, when filtered off, gave positive reactions with Millon reagent

The small amounts of ammonium sulphate precipitates obtained from the above fractions that were insoluble in water did not give any protein reactions, and were almost completely soluble in hydrochloric acid, from which solutions crystals of uric acid were obtained on evaporation

The above data show that the injected material was excreted in the urine in considerable amounts While it did not yield the heat-precipitation test in the urine, it did give a strong reaction in an aqueous solution of the ammonium sulphate precipitate from the urine

Of course these urines contain much less of the injected material corresponding to the Bence Jones substance than is present in cases of "myelopathic albumosuria" Coriat,[9] Hutchinson,[10] Rosin,[11] Simon,[12]

9 Coriat Am Jour Med Sc, 1903, cxxvi, 631

10 Hutchison Am Jour Med Sc, 1903, cxxv, 644

11 Rosin Allg med Centr-Zeit, 1897, lxvi, 1132, Berl klin Wchnschr, 1897, xxxiv, 1044

12 Simon Am Jour Med Sc, 1902, cxxiii, 939

Sussman,[13] Matthes,[14] Rostoski,[15] Ribbinik,[16] Huppert,[17] and Magnus-Levy,[18] have stated that in their cases, although the precipitates were obtained in the urines at low temperature, they did not completely dissolve on continued heating The disappearance of the precipitate after continued heating is not always noted even when the Bence Jones protein is present, as the above-named observers showed, and this reaction is not a true test for the Bence Jones protein We must bear in mind that the influence of salts has a great deal to do with the solution and precipitation of this protein, as is the case with other proteins This fact has been demonstrated by Spiro,[19] Pauli and Rona[20] and Hammarsten[21]

In order to clear up the obscure points relating to the protein excreted in this connection, the following experiment was undertaken to find out what reactions occur on heating a sample of urine (sp gr 1 020) containing an amount of the substance approximately equal to the proportion in which it exists in cases of "myelopathic proteosuria" The aqueous solution of the precipitates obtained from the urine by treatment with ammonium sulphate was dialyzed till free from sulphate and speedily evaporated over a water bath until the liquid had a syrupy consistency When the syrupy solution of the excreted substance was added to the urine in various proportions, no change in the urine took place on heating The treated urine gave marked precipitates with picric acid and trichloracetic acid, however These reactions did not take place before the addition of the excreted substance The precipitates dissolved on further heating and became more marked on cooling

Summary of Results of Procedures B and C

1 After the *subcutaneous* injection of products of *peptic* digestion of osseo-albumoid, the urine in no instance gave the heat-precipitation test, but the urine gave the proteose test on addition of picric acid or trichloracetic acid An aqueous solution of the ammonium sulphate-saturation precipitate gave the heat-precipitation test and the proteose test with picric acid and trichloracetic acid

13 Sussman Dissertation, Berlin, 1897
14 Matthes Kong f inn Med, 1896, xiv, 476
15 Rostoski Deutsch med Wchnschr, 1901, xxvii, 224, Munchen med Wchnschr, 1901, xlviii, 1115, 1902, xlix, 740, Sitz Ber d phys med Gesellsch zu Wurzburg 1901, 31 and 33, 1902, 82
16 Ribbinik Maly's Jahrb d Tierchem, 1892, xxii, 525
17 Huppert Ztschr f phys Chem, 1896 97, xxii, 500, Centralbl f d med Wissensch, 1898, xxxviii, 481, Prag med Wchnschr, 1889, xiv, 35
18 Magnus-Levy Kong f inn Med, 1900, xviii, 496, Ztschr f phys Chem, 1900, xxx, 200
19 Spiro Ztschr f phys Chem, 1900, xxx, 182
20 Pauli and Rona Beitr z chem Phys u Path, 1902, ii, 1
21 Hammarsten Arch f d ges Phys, 1878, xxviii, 65

2 The substance excreted in the urine became insoluble after its precipitation with alcohol, thereby resembling the primary proteins rather than the proteoses

3 The urine from normal dogs often gives a reaction with potassium mercuric iodid that resembles the proteose reaction with this reagent We hope to study the relation between this reaction and the presence of kynurenic acid and "diamins," in dog urine

4 After the *subcutaneous* injection of products obtained by *tryptic* digestion of osseo-albumoid, no heat-precipitation test was obtained in the urine, but the urine gave a good proteose test with picric acid and trichloracetic acid An aqueous solution of the ammonium sulphate-saturation precipitate gave a marked heat-precipitation test and also proteose tests with picric acid and trichloracetic acid

5 When some of the substance excreted in the urine was isolated and its aqueous solution concentrated to a syrupy consistency and added to urine of 1 020 specific gravity in varying proportions, no heat-precipitation test was obtained The urine, however, gave marked tests for proteose with picric acid and trichloracetic acid

6 The injection of these products did not produce any untoward effects

7 It seems fair to assume, on account of the fact that the heat-precipitation test was not obtained in the urine direct but in an aqueous solution of the ammonium sulphate-saturation precipitate from the urine, that if a larger amount of substance had been present, the heat-precipitation test would have been obtained in the *urine* itself

D LEUKOCYTIC PROTEOLYSIS OF OSSEO-ALBUMOID

The original assumption which led to this work was that the proteolytic enzymes in the cells of the new bone-growth, or the unrestrained action of the enzymes from the bone-marrow cells might cause the production of the Bence Jones protein by the transformation of osseo-albumoid It was desirable, therefore, to ascertain what the direct action of the enzymes of leukocytes would be on osseo-albumoid and to learn the results that would occur if the substances produced by their proteolysis were injected into dogs

The method described by Opie[22] was used to obtain the leukocytes and to separate the enzymes from them in a dry, powdered state By this method Opie has shown that an enzyme designated by him "lymphoprotease" is destroyed when present in an acid medium, and that one which he calls "leukoprotease" remains active when contained in an alkaline medium The alkaline condition was favorable for our proposed experiment, as the leukoprotease would, in bone-marrow, normally act in

22 Opie Jour Exper Med , 1906, viii, 410

an alkaline medium Opie[23] has shown also that the enzymes from bone-marrow are identical with those obtained from polynuclear leukocytes with fine granulations, and, since these cells are formed in the bone-marrow, the bone-marrow may be regarded as the source of the enzymes which both contain Furthermore, Opie had shown that the "lympho-protease" is contained in the lymphocytes, and although the greater proportion of the cells in an inflammatory exudate are polynuclears, a number of lymphocytes are present, and by this method of preparation, the enzymic action of the lymphocytes is eliminated

In the experiment described below a portion of osseo-albumoid was treated with a suspension of 2 35 gm of dry powdered "leukoprotease" in saline solution About 800 c c of 0 25 per cent sodium carbonate and 1 c c of toluol were added and the mixture placed in an incubator at 39 C At the end of a week, about one-half of the material was digested [24]

After twelve days' digestion of the osseo-albumoid by the leukocytic material, it was observed that the amount of undigested matter did not diminish on the two succeeding days The mixture was then filtered, and the filtrate neutralized and saturated with ammonium sulphate at the boiling temperature A very large amount of proteose-like material was obtained Even after repeated treatment of this precipitate with water a considerable amount of substance remained insoluble This insoluble portion gave all the protein color-reactions, but no proteose tests, and proved to be metaprotein That portion of the precipitate which was soluble in water was dialyzed free from sulphate and concentrated speedily by evaporation at 40 C On heating an aqueous solution of the above precipitate a marked cloudiness was produced, which was not changed on further heating, nor by the addition of acid

With picric acid, trichloracetic acid and potassium mercuric iodid, the solution gave very abundant precipitates which dissolved almost completely on further heating and reappeared on cooling On addition of concentrated nitric acid a precipitate was produced which dissolved completely on heating and returned on cooling

The extract of leukocytes did not yield a precipitate on heating, nor when allowed to undergo autolysis under toluol On saturating this autolyzed extract with ammonium sulphate a small amount of precipitate came down, which, after solution in water, did not respond to the heat-precipitation test

23 Opie Jour Exper Med, 1905, vii, 759

24 The following references to enzymes from leukocytes may be noted
Longcope and Donhauser Jour Exper Med, 1908, x, 618
Opie ibid, 1905, vii, 316 and 759, 1906, viii, 410 and 536 Opie and Baker ibid, 1907, ix, 207
Jochmann Ztschr f Hyg u Infektionskrankh, 1908, lxi, 71
Jochmann and Lockemann Beitr z chem Phys u Path, 1902, ii 449
Jochmann and Muller Munchen med Wchnschr, 1906, liii, 1392, 1507 and 2002, Verhandl d Kong f inn Med, Wiesbaden, 1907

The osseo-albumoid that was not digested after two weeks' treatment with the dried leukocytic product was transferred to a fresh saline extract of leukocytes and placed under toluol in an incubator

A residue remained after two weeks' digestion in this fresh saline extract of leukocytes The residue was filtered off, the filtrate saturated with ammonium sulphate at the boiling temperature and an abundant proteose precipitate obtained, which dissolved readily in water forming a dark brown solution On heating this solution an abundant precipitate came down which dissolved to a slight extent on further heating, but which apparently was fully restored on cooling Practically the same results were obtained with picric acid, trichloracetic acid and potassium mercuric iodid With nitric acid an abundant precipitate was produced, which disappeared on heating and returned on cooling The solution was dialyzed till free from sulphate and evaporated speedily to dryness at 40 C As it was thought that the undigested material might be collagen, it was boiled with water but the supernatant liquid gave only a slight reaction for protein.

To determine if this residue was digestible it was treated with a fresh active alkaline trypsin mixture and placed in an incubator After forty-eight hours no digestion had taken place, and on saturation with ammonium sulphate, no precipitate came down Most of the undigested material dissolved in dilute sodium carbonate, from which it could be precipitated by acidifying the alkaline solution with hydrochloric acid This material consisted chiefly of hematin, as seemed evident from its color

Summary of Results of Procedure D

1 Osseo-albuminoid, on digestion with a dried extract of *leukocytes,* prepared by the method of Opie, yielded osseo-albumoses

2 An aqueous solution of the *osseo-albumoses* produced by the leukocytic proteolysis of osseo-albumoid did not give a sharp heat-precipitation test After the addition of picric acid, trichloracetic acid, nitric acid or potassium mercuric iodid, however, a sharp proteose-test was obtained

3 Neither the extract of leukocytes nor the autolyzed leukocytic material gave a heat-precipitation test

E SUBCUTANEOUS INJECTION OF PRODUCTS OBTAINED IN THE LEUKOCYTIC PROTEOLYSIS OF OSSEO-ALBUMOID

Of the proteose-like product (D), 2 3060 gm were dissolved in 11 c c of 0 85 per cent sodium chlorid This solution was injected subcutaneously into a bitch, the subject of a former experiment The weight of the dog was 7 kilos The amount of the substance injected per kilo of dog's weight was 0 33 gm Injection occurred at 11 a m , March 16, 1909 No untoward effects were noticed None of the fractions of urine

following the injection gave a precipitate on heating Fraction 2 yielded heavy precipitates with picric acid and trichloracetic acids, but the precipitates did not dissolve completely on continued heating On cooling, much of the precipitate in each was restored With potassium mercuric iodid all fractions gave a precipitate, this being specially marked in Fraction 2 The precipitate was not completely soluble after continued heating but was restored on cooling The fractions were obtained twenty-four, forty-eight, seventy-two, ninety-six and 120 hours after the injection

The several fractions of urine from this dog were saturated with ammonium sulphate at the boiling temperature Fractions 2, 4 and 5 gave fair amounts of precipitates These precipitates were found to be very slightly, if at all, soluble in water They were *insoluble* in sodium chlorid, 0 2 per cent hydrochloric acid and ethyl alcohol, but soluble in 0 5 per cent sodium carbonate The insoluble material gave very marked responses to the Millon and xanthoproteic tests The filtrate from the material insoluble in water gave no reactions with picric acid, Millon reagent or potassium mercuric iodid

It was thought that this excreted substance might be phosphoprotein Some of the original urine was therefore rendered amphoteric to litmus, heated to boiling and, while briskly boiling, was treated with acetic acid drop by drop A white, flaky precipitate was produced, which was filtered off It gave the following reactions

1 Soluble in excess of 0 2 per cent hydrochloric acid

2 On being boiled with 2 per cent hydrochloric acid until a dark color was produced, then neutralized and tested for reducing substance with Fehling solution, no reduction was obtained

3 It gave a positive test for phosphates on evaporation, *fusion with* sodium carbonate and sodium nitrate, and treatment with dilute nitric acid and ammonium molybdate solution The original precipitate was washed till the washings gave no test for phosphates before the fusion was made

These results show that the substance excreted was probably phosphoprotein No substance giving these reactions of phosphoprotein was obtained from the urine before the injection of the leuko-proteolytic product of osseo-albumoid Evidently, the injected product was either modified in some way or phosphoprotein present in it was excreted as such, while the rest of the material was retained

F INTRAVENOUS INJECTION OF PRODUCTS OBTAINED IN THE LEUKOCYTIC PROTEOLYSIS OF OSSEO-ALBUMOID

EXPERIMENT 1.—Of the proteose-like product (D), 0 865 gm was dissolved in 30 c c of 0 85 per cent sodium chlorid solution This was injected intravenously into a dog, the subject of a previous experiment, at the rate of 1 c c

a minute, March 23, 1909 The animal was under the influence of ether during the injection procedure No untoward symptoms developed

The first fraction of urine following the injection gave a marked cloudiness on heating which remained on continued heating and after addition of acid and dilution Picric acid and trichloracetic acids produced slight precipitates which disappeared on heating and returned on cooling The second fraction gave the same reactions but they were slighter in degree Potassium mercuric iodid produced a precipitate which did not clear completely after continued heating but was restored on cooling The fractions were obtained twelve, thirty-six, sixty, and eighty-four hours after the injection

The fractions of urine from this dog were saturated with ammonium sulphate at the boiling temperatures and the precipitates dissolved in water Fraction 1, on heating, gave a slight cloudiness which was not changed by continued heating, by acid, by potassium mercuric iodid or by dilution With picric and trichloracetic acids it gave abundant precipitates which did not completely dissolve on further heating but were restored on cooling

The results of this experiment show that when the substance reached the blood-stream it was excreted unchanged through the kidneys, and when present in sufficient quantities in the urine it gave a fair heat-precipitation test and marked reactions with picric and trichloracetic acids

Of course, it must be remembered that the amount of substance that was present in the fractions of urine was quite small in comparison with the amounts excreted in "myelopathic proteosuria" Possibly, in the presence of larger amounts of the substance, the heat reaction would have been more marked

The subject of this experiment was accidentally killed a week later during the development of anesthesia while preparation was being made for another intravenous injection At autopsy a hemorrhagic peritonitis was found with about 50 c c of blood in the peritoneal cavity

EXPERIMENT 2.—Of the proteose-like product (D), 0 4 gm was dissolved in a small volume of physiological salt solution and injected intravenously into a dog at 2 p m , March 30, 1909

The first and second urinary fractions following the injection gave a marked cloudiness on heating, which did not disappear on continued heating, nor after addition of acid or on dilution With picric and trichloracetic acids and with potassium mercuric iodid, each fraction gave a slight precipitate which dissolved on heating and was restored on cooling The fractions were obtained twelve, thirty-six, sixty, and eighty-four hours following the infusion

The fractions of urine from this dog were saturated with ammonium sulphate at the boiling temperatures The precipitates were dissolved in water and tested with the following results Fractions 1 and 2 gave a cloudiness on heating which did not change on continued heating, on dilution, or on addition of acid With picric and trichloracetic acids and potassium mercuric iodid each fraction gave slight precipitates which did not completely dissolve on heating

The result of this experiment confirms that of the previous one The injected substance was excreted in the urine, giving a fair heat-precipitation test, and marked picric and trichloracetic acid tests, both in the

urine itself and in the solution of the ammonium sulphate-saturation precipitate from the urine The substance excreted in the urine under these conditions, unlike that after subcutaneous injection, was not phosphoprotein It was like proteose in its responses to the tests employed

Summary of Results of Procedures E to F

1 After the *subcutaneous* injection of an aqueous solution of the product obtained by the *leukocytic* proteolysis of osseo-albumoid (D), the urine did not give the heat-precipitation test, but did give proteose tests with picric acid and trichloracetic acid

2 The substance excreted in the above case was probably phosphoprotein either present in the injected material to begin with and excreted unchanged, or formed from the substance injected

3 After *intravenous* injections of aqueous solutions of the product obtained by the *leukocytic* proteolysis of osseo-albumoid the urine gave a fair heat-precipitation test and marked proteose tests with picric acid and trichloracetic acid

4 The substance excreted after the intravenous injections was apparently proteose and not phosphoprotein

5 In no case did the injected substance produce untoward symptoms

6 The results of the heat-precipitation test following intravenous injections suggest that *possibly* the Bence Jones protein is formed by the action of enzymes of the bone-marrow on osseo-albumoid, and that this product of their action is eliminated through the kidneys after it reaches the blood-stream

G INTRAPERITONEAL INJECTION OF OSSEO-ALBUMOID

One gram of osseo albumoid, prepared by Hawk and Gies for elementary analysis, was suspended in water The mixture was heated to boiling, cooled and injected intraperitoneally into a large dog, at 3 p m, March 25, 1909

The fractions of urine following the injection did not contain any proteose-like material but they contained a small amount of serum protein

The urine before injection gave no reaction with picric acid or trichloracetic acid On saturation with ammonium sulphate a small amount of a dark granular precipitate was obtained that consisted of urates, urobilin, and a small amount of an insoluble residue which gave no reaction for protein

On March 30, the dog died and, on autopsy, a very intense hemorrhagic peritonitis was found with over a liter of bloody fluid in the peritoneum No proteose could be detected in this fluid It was hoped that in the experiment just described, the osseo albumoid would cause an inflammatory reaction and then undergo a proteolysis occasioned by the enzymes of the leukocytes in the exudate and that the product of this digestive action would be taken up by the blood and undergo excretion Such conditions would bring about a more natural leukocytic proteolysis of osseo albumoid and would effect a process more nearly comparable to that supposedly taking place in multiple myeloma On account of the danger of the intraperitoneal injection, it was decided to attempt to induce more favorable conditions by making an *intrapleural* injection of osseo albumoid as described below

H INTRAPLEURAL INJECTION OF OSSEO-ALBUMOID

Osseo albumoid, 0 4 gm , from the same product as that used for the intra-peritoneal injection, was suspended in 10 c c of physiological salt solution, heated to boiling, cooled, and injected into the left pleural cavity of a dog, at 4 p m , April 3, 1909

The fractions of urine following this injection did not give any precipitate on heating or after addition of picric and trichloracetic acids With potassium mercuric iodid a precipitate was produced which did not disappear on heating The fractions were obtained nineteen, forty-three, sixty seven and ninety-one hours after the injection and then every twenty-four hours for one week

All the fractions of urine from this dog were saturated with ammonium sulphate but Fraction 4 (April 7) was the only one that gave a proteose like precipitate A solution of this precipitate gave a positive reaction for proteose when tested with potassium mercuric iodid, picric acid and trichloracetic acid When an aqueous solution of the precipitate produced by ammonium sulphate was heated, a marked turbidity ensued that did not disappear completely after continued heating, and was more marked on cooling

On April 17, two weeks after the intrapleural injection, the dog was killed At autopsy the left lung and pleura were found to be normal, with no evidence of any osseo-albumoid present

The results of the tests on the urine in this experiment indicate that the injected osseo-albumoid was taken up by the blood and the substance excreted In one fraction of the urine, obtained four days after the injection, a substance was present which was precipitated by picric acid, the product thus thrown down dissolving on warming and reappearing on cooling — apparently proteose

Summary of Results of Procedures G to H

1 *Intraperitoneal* injection of osseo-albumoid, as a method for the production of the autolytic derivatives of osseo-albumoid in the exudate resulting from its injection, is apparently too unsatisfactory a process for use in such experiments

2 The urine, four days after the *intrapleural* injection of *osseo-albumoid,* yielded an ammonium sulphate-saturation precipitate whose aqueous solution gave a pronounced heat-precipitation test and marked proteose reactions with picric acid and trichloracetic acid

3 SUMMARY OF GENERAL CONCLUSIONS

1 The peptic digestion of osseo-albumoid yielded a water-soluble substance precipitable by saturation with ammonium sulphate In one instance this material gave a heat-precipitation test, but the reaction was not as marked in its sharpness as the same test when applied to elastose Negative results were obtained when the test was applied to two other similar products obtained in the peptic digestion of osseo-albumoid

2 After the subcutaneous injection of the material produced by the peptic digestion of osseo-albumoid, the urine did not yield a heat-precipitation test, but gave a positive reaction with picric and trichloracetic

acids The ammonium sulphate precipitate from the urine in this experiment gave positive heat as well as picric acid and trichloracetic acid tests

3 The heat-precipitation test in the urine is determined by the amount of substance excreted as well as by the reaction of the urine and the *quantity of salts present*

4 After the subcutaneous injection of the material produced by the peptic digestion of osseo-albumoid, an alcoholic precipitate of the substance excreted in the urine was rendered insoluble on standing under alcohol, thereby showing one of the characteristics of the Bence Jones protein, and departing from the usual properties of proteoses

5 After the subcutaneous injection of the substance obtained by the tryptic digestion of osseo-albumoid, it was excreted by the urine but it did not give a heat-precipitation test

6 Osseo-albumoid undergoes proteolysis when subjected to the action of the enzyme of leukocytes that acts in alkaline media A solution of the ammonium sulphate precipitate of this digestive mixture gave a heat-precipitation test as well as reactions with picric acid and trichloracetic acid

7 The material produced by the leukocytic proteolysis of osseo-albumoid, after its *subcutaneous* injection, was found to have been modified in the body and was excreted in the urine, in whole or in part, as a substance resembling phosphoprotein

8 Intraperitoneal injection could not be used as a satisfactory method of favoring autolysis of osseo-albumoid on account of the peritonitis produced

9 Osseo-albumoid was absorbed, after its intrapleural injection, and a digestive product of it was excreted in the urine This product in the urine did not give a heat-precipitation test, but a solution of the ammonium sulphate precipitate from the urine gave this reaction as well as one with picric acid and trichloracetic acid

10 Some of the results indicate that the Bence Jones protein *may be* formed from osseo-albumoid by the action of enzymes in diseased bone, although further research will be necessary to confirm this opinion

It gives me great pleasure to thank Professor William J Gies for suggesting this problem and for his constant supervision of the work

NOTE —A complete bibliography was given by Rosenbloom in a dissertation entitled "A Contribution to the Study of the Nature and Origin of the Bence Jones Protein," submitted to Columbia University in 1909, also Biochem Bull, 1911, 1, 161

437 West Fifty-Ninth Street

SPONTANEOUSLY PRECIPITATED BENCE JONES PROTEIN IN URINE*

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In another paper[1] I have reviewed the various theories which have been proposed regarding the origin of Bence Jones protein In the paper preceding this one I have described experiments which, conducted under the direction of Prof W J Gies, were planned to determine whether osseo-albumoid, a constituent of bone, is a precursor of Bence Jones protein That inquiry warranted the conclusion that the Bence Jones protein *may be* formed from osseo-albumoid by the action of enzymes in diseased bone

The chemical nature of Bence Jones protein has been thoroughly studied, but very little is known regarding the mode of formation of this important substance Weber and Ledgingham[2] have suggested that the cytoplasmic residue of karyolyzed plasma cells is the source of Bence Jones protein If this view is correct, the endogenous purins of the urine should be supernormal in amount owing to increased nuclear destruction Preparations were made for a thorough inquiry into this particular phase of the subject through study of the urine of a patient with multiple myeloma The patient died, however, before the work was well under way Considerable Bence Jones protein was available, nevertheless, and a number of facts of chemical interest, which were noted, are mentioned below

General Description of the Urine

The twenty-four hour urine was examined daily for a period of eight days During this period it was noticed that with but one exception, about one-third the bulk of each specimen was occupied by a pinkish

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* The clinical history and findings of this case were those of multiple myeloma The writer wishes to thank Dr Davison under whose service at Mt Sinai Hospital the patient was observed It is also a pleasure to acknowledge the hearty cooperation obtained from Drs Bookman, Crohn, Mandlebaum and Munker

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1 Rosenbloom Biochem Bull, 1911, i, 161

2 Weber and Ledgingham Proc Roy Soc Med, Path Sect, 1909, ii, 193, Folia hematol, 1909, viii, 14

sediment, which, after removal by filtration, was found to give all the reactions typical of Bence Jones protein.[3]

The volumes of the daily urines varied between 1,200 c c and 1,450 c c On heating the filtered urine a precipitate was produced at from 50 to 51 C The precipitate increased in bulk on heating to 55 C At 56 C the precipitate flocculated in a clear surrounding liquid At 78 C, solution of the precipitate began At 90 C, complete solution of the precipitate occurred As the heated urine cooled, the precipitate reappeared

Such clear-cut heat-precipitation was not always obtainable at the temperatures indicated In some of the urine the precipitate would not completely dissolve at the highest temperatures The temperature of *initial* coagulation also varied The first signs of turbidity were always obtained at a temperature between 51 and 55 C, and solution of the precipitate began at a temperature between 78 and 81 C

When the urines were made alkaline with sodium hydroxid, heat failed to induce precipitation, but after acidification of such alkalized urine, heat-precipitation could be elicited

Nitric acid solution (25 per cent), when added in small quantity to the fresh urine, caused cloudiness On shaking the mixture the turbidity disappeared The addition of a chemical excess of the acid produced an abundant precipitate When the acid mixture was heated the precipitate dissolved This precipitate was insoluble in a physical excess of the acid Hydrochloric and sulphuric acids gave the same reaction Picric, tannic, phosphotungstic, sulphosalicylic and metaphosphoric acids produced precipitates but the corresponding precipitates did not dissolve completely when the mixtures were heated The addition of two volumes of alcohol to the urine caused complete precipitation of the reactive substance This precipitate was soluble in water but, when immersed in alcohol for a week, it became insoluble in water

Saturation of the urine with sodium chlorid failed to effect precipitation but, on heating this saturated solution, an abundant precipitate was produced The precipitate did not dissolve on further heating Saturation of the urine with magnesium sulphate, after making the urine acid, caused heavy precipitation This precipitate did not dissolve when the mixture was boiled On saturating the neutralized urine with ammonium sulphate, and also on saturating the acid urine with sodium sulphate, complete precipitation of protein occurred

Serum protein was absent from the urine of this patient during the period of observation The amount of the heat-precipitable protein which

3 Bradshaw (Trans Med-Chir Soc, Lond, 1898, lxxxi, 259, Brit Med Jour, 1898, i, 1136) has described a similar case in which the substance was spontaneously precipitated Williams (Biochem Jour, 1910, v 225) described urine containing Bence Jones protein, and stated that on several occasions the urine was milky when voided He did not say whether the milkiness was due to Bence Jones protein

was excreted in twenty-four hours varied from 3 to 5 gm It contained from 8 to 15 per cent of the total nitrogen

Chemical Data on the Substance Isolated from the Urine

The purified, heat-precipitable protein was obtained from the urine by the following method The urine was heated slowly to 60 C and the precipitate filtered off (This coagulation was so complete that the filtrate gave no protein reactions) The precipitate was washed with cold water, dissolved by means of 0 5 per cent sodium carbonate solution and precipitated from this solution by alcohol The precipitate was dialyzed in running water for a week, then washed with absolute alcohol and ether, and dried at 105 C The substance prepared by this method had the general appearance of dry egg-albumin It was insoluble in water but dissolved in dilute alkali

The nitrogen content of this material varied between 15 08 per cent and 15 24 per cent The sulphur content varied between 1 12 per cent and 1 25 per cent Phosphorus was absent The purified material responded to the following tests Millon, Liebermann, biuret, xanthroproteic, Adamkiewicz, and Molisch In peptic digestion it yielded protoproteose, secondary proteoses, and peptone, but no heteroproteose A solution of the purified substance in 0 5 per cent sodium carbonate did not give the heat-precipitation test, but on the addition of sufficient saline material and acid, this test could be obtained

These facts make it evident that the material under investigation was true Bence Jones protein

A SIMPLE INSTRUMENT FOR DETERMINING THE COAGULATION-TIME OF THE BLOOD *

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The accuracy of most methods for determining the coagulation-time of the blood depends on three main factors

1 The sharpness with which the end-point appears

2 Constancy between the volume of blood used for the test and its area of exposure to foreign surface

3 Constancy of temperature

These three factors have been considered in the following modification of Milian's ingenious method[1] and, it is believed, make it as accurate as any method at present in use

The instrument consists of a slide on which are mounted with balsam two glass disks 5 mm in diameter

METHOD[2]

Anoint the surface from which the blood is to be obtained with a thin layer of petrolatum (This prevents contact of the blood with the skin and avoids thereby a slight source of error) Prick the skin through the petrolatum, obtaining, if possible, a free flow of blood Wipe away the first drop of blood which appears Touch the surfaces of the glass disks to the next drops in such a way that each disk is completely covered with blood As a rule one of the drops obtained in this way will have approximately the depth of those shown in the figure If not, the slide must be washed and fresh drops obtained Having obtained drops of the correct depth, invert the slide over a glass nearly filled with water at a temperature of 40 C and cover it with a sponge or folded cloth wet with water at the same temperature By this means the blood is kept in a moist chamber at a temperature of about 38 C (To prevent cooling the glass may be kept in a water bath at 40 C) After five minutes have elapsed remove the slide at intervals of one minute, hold it in a vertical position in front of a white surface, and note the surface contour of the drops of

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*This method has been briefly outlined by me in a previous article "The Relation of Blood-Platelets to Hemorrhagic Disease," Jour Am Med Assn, 1910, lv, 1185

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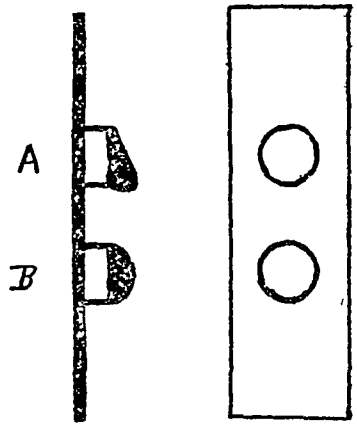
1 Milian, G Technique pour l'étude clinique de la coagulation du sang, Bull et mém Soc méd d hôp de Paris, July 5, 1901

2 This instrument will be made by Carl Zeiss, Jena, and can be obtained in America from his agents, Eimer & Amend, 205 Third Ave, New York

blood So long as the blood is fluid the drops hang down assuming the shape shown in the figure (A) After coagulation has proceeded to a certain degree the drops fail to change in shape when the slide is tilted but maintain a spherical contour This is taken as the end-point It appears sharply and is easy to determine The coagulation-time as determined by this method, counting from the time of appearance of the blood, varies in normal cases from six to nine minutes Under pathologic conditions it may be as great as forty minutes



Instrument for determining the coagulation time A, contour of drop when blood is fluid B, contour of drop when blood is clotted—end-point

With this instrument the coagulation-time can be determined comparatively, that is, blood from a patient can be taken up on one disk, blood from a normal individual on the other, the two coagulation-times can then be determined simultaneously and the results compared When this procedure is followed it is necessary that the two drops have approximately the same depth The careful regulation of temperature is here, however, not so necessary, and it suffices to invert the slide over a glass of warm water and cover it with the hand When both specimens of blood are normal they usually reach the end-point within two minutes of each other When one specimen has a delayed coagulation-time it may remain fluid more than five times as long as the normal

The coagulation-time determined by this method represents neither the time at which coagulation begins nor the time at which coagulation is complete The former point is evident, for strands of fibrin can be removed from the blood with a needle before the end-point is reached The latter point is shown by the fact that the coagulation-time in animals poisoned with chloroform (a condition in which the fibrinogen content of the blood may be enormously reduced) may be normal, even when the fibrinogen content of the blood is considerably reduced Evidently, then, normal blood may become firm enough to give our arbitrary end-point before all its fibrinogen is transformed into fibrin

The sources of error for the method are comparatively small when blood used for the determination is obtained with perfect technic The

chief source of error lies in the using of drops of incorrect depth If the drop is extremely shallow coagulation is markedly accelerated If on the other hand, the drop is extremely deep, retraction of clot and extrusion of serum may interfere with correct determination of the end-point I have noted that by varying the depth of drops of normal blood, from a thin film to the deepest drop which can hang from the disks, the coagulation-time can be made to vary from two minutes to ten or eleven minutes Such a gross source of error as this, however, does not come practically into consideration and as a rule several drops as ordinarily picked up, clot within two minutes of each other

This method is a modification of Milian's method Milian allowed drops of blood to fall on the glass slide and at known temperature determined the end-point by occasionally holding the slide in a vertical position and noting the change in contour of the drops Hinman and Sladen[3] recognized the source of error of Milian's method due to the lack of constancy in the diameter of the drops of blood used and in their paper suggest the use of drops 4 to 5 mm in diameter They offer their method as a rough means for determining the coagulation-time for which no instrument is needed In Hinman and Sladen's method are two serious sources of error One is due to lack of constancy in the depth of the drops used the other, to lack of constancy of temperature These investigators recognize the marked influence of temperature on coagulation, but consider that such variation as occurs in hospital wards is not great enough to be of serious moment This may be true when the blood tested is normal When the coagulation-time is delayed, however, its variation with temperature is much greater and is a source of error which cannot be overlooked We have noted, for example, that the coagulation-time of a specimen of normal blood at temperatures of 38, 30 and 20 C was nine minutes, fifteen minutes and twenty-five minutes, respectively At the same temperatures blood from a patient with mild hemophilia gave coagulation-times of sixteen minutes, twenty-four minutes and sixty minutes, respectively The pathologic blood as compared with the normal showed, then at 38 C a comparatively small delay (seven minutes) while at 20 C it showed a great delay (thirty-five minutes) Unfortunately by neither Milian's nor Hinman and Sladen's method can the determination be made at 38 C by the simple procedure of inverting the slide over a glass of warm water Unless the blood hangs from elevated disks the condensation of moisture on the slide causes it invariably to flow off

Only such sources of error as are directly concerned in the use of the instrument have been mentioned in this paper For discussion of sources of error connected with the obtaining of blood the reader is

3 Hinman, F, and Sladen, F J Measurement of the Coagulation Time of the Blood and its Application Bull Johns Hopkins Hosp, 1907, xviii, 207

referred to papers by Pratt,[4] Milian,[5] Hinman and Sladen,[3] etc The latter sources of error are sometimes difficult or almost impossible to avoid When the blood tested is flowing freely and is slightly exposed to dirt, injured tissue, etc (as can be accomplished in animals by cutting the ear-vein), numerous determinations may vary less than two minutes When capillary blood is used, however, and especially when blood fails to flow freely and must be expressed from the tissues, constant results are difficult to obtain and duplicate determinations may vary four minutes or more

In conclusion I wish to express my thanks to Dr G H Whipple, associate professor of pathology, Johns Hopkins University, and to Privatdozent N R von Jagic of the von Noorden clinic, Vienna, where this study was completed

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4 Pratt, J H Beobachtung uber die Gerinnungzeit des Blutes und die Blutplattchen, Arch f exper Path u Pharmakol, 1903, v, 49, p 299

5 Milian, G Les causes d'erreur, dans l'étude clinique de la coagulabilité du sang, Presse méd, 1904, No 26

THE NEUROSEROLOGICAL FINDINGS IN TABES, GENERAL PARESIS, CEREBROSPINAL SYPHILIS, AND OTHER NERVOUS AND MENTAL DISEASES*

D M KAPLAN, M D, AND LOUIS CASAMAJOR, M D
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This communication is the record of a laboratory equipped for serological work It does not concern itself with the post-mortem findings, nor does it attempt to discuss the clinical distinctions of the diseases scheduled The material was obtained from the Neurological Institute and in a measure from the Manhattan State Hospital, Ward's Island The interesting work of Plaut has shown the necessity of a more definite laboratory knowledge of tabes, general paresis and cerebrospinal lues In the above mentioned work there is little to help one in the differentiation between difficult cases of paresis and cerebrospinal syphilis, nor do other writers shed much light on the situation from a laboratory standpoint The material analyzed in this communication, 340 cerebrospinal fluids and as many serums, we have divided into four groups or types

1 The negative types
2 The positive types
3 The aberrant types
4 The post-therapeutic types

Before going into a consideration of these various types, we will give a brief outline of the technic employed

TECHNIC

The Wassermann Reaction —This was performed on both the serums and the spinal fluids Of the latter 0 5 c c was used The serums were kept on ice and, as a rule, were not older than forty-eight hours The original Wassermann technic was adhered to, besides this, an alcoholic beef-liver extract was also used The watery extract of a syphilitic fetal liver was obtained by shaking the finely divided liver-pulp in the Spiegelberg shaking apparatus for twenty-four hours The fluid obtained after centrifuging was standardized The serums used for standardization purposes came from known positive cases of tabes, general paresis and lues cerebrospinalis No further comment need be made concerning this test, as it conforms in detail to the method employed in Berlin

The Globulin Test —The precise nature of the protein contained in the cerebrospinal fluid has never been definitely settled and it is outside

*From the laboratory of the Neurological Institute, New York

of the scope of this paper to discuss the question We shall speak of this substance as globulin according to the accepted custom The method of gauging an excess was described by one of us,[1] but a slight change in the original technic was made in that 0 9 per cent salt solution was added to each tube containing less than 0 5 c c of spinal fluid, in order to bring it up to that quantity The remaining technic was as in the original text The test tubes used were 1 cm in diameter

The Cell-Count—The Fuchs-Rosenthal method alone was used. We know of no reason why this method should not be used more extensively, as it is the only method, to our knowledge, capable of giving a quantitative insight into the cellular content of the cerebrospinal fluid

The Fehling Test—Half a cubic centimeter of Fehling's solution is diluted with an equal quantity of distilled water and boiled To the hot fluid is added 0 5 c c of the spinal fluid at a time, until 1 c c is added, boiling after each addition Set aside to cool and observe after a few minutes If the reducing substance is present, the cuprous salt will be deposited in the bottom of the tube A tube of the same size is to be used as in the globulin tests In fluids in which no reduction is obtainable, a violet color develops instead The significance of this will be considered later

PRELIMINARY CONSIDERATIONS

In a negative serological report Fehling's reducing substance is always present In such a report an excess of globulin, as in the method described, is not obtainable The cells in the cerebrospinal fluid should not exceed seven per cubic millimeter and the Wassermann reaction is always negative From an analysis of over 1,000 fluids,[2] we have come to regard seven cells as the upper limit in normal fluids The Wassermann reaction on the serum alone has but little bearing on the serological report It may be negative or positive without changing the positive or negative nature of the report, as the Wassermann test need not bear a direct relation to the pathological processes in the cerebrospinal system

A positive report has any of the following abnormalities an excess of globulin, a positive Wassermann reaction in the cerebrospinal fluid, a cell count of over 7 per c mm, or an absence of Fehling's reducing substance Singly or collectively, when present in the cerebrospinal fluid, they constitute a positive serological report It does not matter whether the serum Wassermann be positive or negative

Our types were the result of a study of the behavior of the largest percentage of cases of the diseases as scheduled, and consequently a

1 Kaplan New York Med Rec, 1910 lxxviii, 1187

2 Kaplan Neurological Serology Jour Nerv and Ment Dis, 1911, xxxviii, No 6

deviation from the majority type makes the result atypical or aberrant This deviation, however, should not be the outcome of therapy It therefore becomes indispensable to know exactly what treatment was given and for how long, before an opinion is finally submitted At times the clinical diagnosis differed from the serological, in such a case the report was considered for the time being aberrant, until the subsequent evidence pointed out the true diagnosis Excluding the effects of therapy, an absolutely negative report is encountered in general paresis and in cerebrospinal syphilis with extreme rarity In tabes dorsalis this is sometimes seen without any treatment, but in the other two diseases it is advisable to wait for further signs before a final diagnosis is agreed on A number of absolutely negative findings were due to the effects of treatment, as previous reports on these cases had shown distinct positive findings

THE NEGATIVE TYPES

In this collection of clinical material it is accepted that syphilis plays no part in the etiology of the neurological disorder Syphilis not involving the nervous apparatus is not infrequently encountered in nervous diseases and should receive separate consideration It is understood that in the negative types the Wassermann reaction in the cerebrospinal fluid is negative, there is no globulin excess, Fehling reduction is present, and the number of cells does not exceed 7 per c mm

Multiple sclerosis is preeminently a nervous disease of the negative type It conforms to the rule formulated above, although two of our cases gave positive Wassermann reactions in the serum It is to be borne in mind that a sufferer from this disease may, at a subsequent date, contract lues, and in such a case the physician's attention should be directed to the time of onset of the multiple sclerosis to establish its relation to the syphilis In amyotrophic lateral sclerosis the serological report is always negative, as likewise in progressive muscular atrophy and in paralysis agitans There are a number of diseases besides those mentioned above, which clinically are frequently confused with cerebrospinal syphilis, in such cases the performance of a serological investigation will often establish the diagnosis The chief value of this work is the grouping of nervous affections into negative and positive serological types Having grouped the disease, its classification is rendered much less difficult and its treatment more accurate The differential diagnosis of diseases belonging to the same group receives no help from the study of a neuroserological report An atypical multiple sclerosis cannot be differentiated from an aberrant amyotrophic lateral sclerosis, as they are both diseases of the negative serological type The same difficulties are at times encountered in positive serological types, as general paresis frequently gives the same serological picture as tabes Fortunately,

wever, the laboratory is rarely called on to furnish all the evidence cessary to make a diagnosis

COMMENTS

The diagnosis of two cases of multiple sclerosis which gave positive assermann reactions was, on closer study, changed to spinal lues. In ese instances a mild excess of globulin was also obtained and the mber of cells in one case was over 100, a condition never encountered disseminated sclerosis In some of the cord tumor cases, heating the inal fluid gave rise to an intense coagulation but these did not show a sitive cell-count In one tumor case there was a cell count of eighteen

TABLE 1.—NEGATIVE SEROLOGICAL TYPES

	No Cases	Serum Wass		Cerebrospinal Fluid				
				Wass		Cells	Globulin	Fehling Red
		+	—	+	—			
sclerosis	12	2	10	0	12	0– 7	Normal	All reduce
e muscular atrophy	3	0	3	0	3	0– 3	Normal	All reduce
hic lateral sclerosis	4	0	4	0	4	0– 4	Normal	All reduce
agitans	5	0	5	0	5	0– 3	Normal	All reduce
a								
otic	4	1	3	0	4	0– 4	Normal	All reduce
hagic	5	0	5	0	5	0– 6	Normal	All reduce
ıterioscleiosis	5	0	5	0	5	0– 4	Normal	All reduce
umors	5	0	5	0	5	0– 6	Normal	All reduce
rd tumors	8	0	8	0	8	0– 4	Normal	All reduce
ydrocephalus	4	0	4	0	4	0– 7	Normal	All reduce
	26	3	23	0	26	0–26		All reduce
elia	3	0	3	0	3	0– 4	Normal	All reduce
tis	4	0	4	0	4	0– 7	Normal	All reduce
	2	0	2	0	2	0– 1	Normal	All reduce
itis lumbalis	1	0	1	0	1	2	Normal	All reduce
elalgia	2	0	2	0	2	0	Normal	All reduce
mia	6	0	6	0	6	0– 5	Normal	All reduce
ia gravis	1	0	1	0	1	2	Normal	All reduce
bia	1			0	1	5	Normal	All reduce
e family idiocy	2	0	2	0	2	2	Normal	All reduce
PSYCHOSES								
	3	0	3	0	3	5	Normal	All reduce
e	2		2		2	0–14	Normal	All reduce
	10	1	9	0	10	5	Normal	All reduce
l	2	0	2	0	2	1	Normal	All reduce
præcox	9	2	7	0	9	1	Normal	All reduce
mentia	5	0	5	0	5	3	Normal	All reduce
pressive insanity	4	0	4	0	4	5	Normal	All reduce
	2	0	2	0	2	3	Normal	All reduce
depression	2	0	2	0	2	0	Normal	All reduce

mphocytes together with a few polynuclears, but no globulin excess ne case of endothelioma of the cord showed a marked xanthochromia id a globulin excess Another showed the same discoloration and an sence of Fehling's reduction The majority of them, however, gave egative results

In the case of epilepsy with the twenty-three cells and the positive Wassermann in the serum, the etiology is probably syphilis One patient ith polyneuritis had at first been diagnosed tabes Two of the six euiasthenics were for a time thought to be paretics One of the two ositive dementia præcox cases gave a luetic history It is to be noted hat the case of hydrophobia showed a very marked Fehling's reduction n one case of recent hemiplegia due to hemorrhage, a cell count of enty-seven and a mild globulin excess was obtained

It is quite certain that this material does not exhaust this class of cases It is still unknown to what extent the acute exanthemata affect the cerebrospinal fluid The time is near when no neurological status will be considered complete without a serological study of the case

It is evident from the above that the number of neurological diseases with negative serological findings is very large indeed The report is of value from a standpoint of differential diagnosis, where one is confronted, for instance, with the differentiation between a general paresis and a traumatic psychosis, or a cerebrospinal syphilis and a disseminated sclerosis Diseases of a positive type cannot be confused with those of a negative nature after a proper serological study

THE POSITIVE TYPE

In offering these classifications clinical distinctions were not taken into consideration The types, as offered, are the result of study of the

TABLE 2.—POSITIVE SEROLOGICAL TYPES

	No Cases	Serum Wass +	Serum Wass —	Cerebrospinal Fluid Wass +	Cerebrospinal Fluid Wass —	Cells	Globulin	Fehling Red
General paresis	60	60	0	60	0	8–78	Excess	Reduce
Cerebrospinal syphilis (Plaut type)	30	28	2	0	30	96–451	Excess	Not all reduce
Cerebrospinal syphilis (positive type)	16	15	1	16	0	94–248	Excess	All reduce
Tabes dorsalis (hyperlymphocytic type)	8	4	4	4	4	64–98	No excess	All reduce
Tabes dorsalis (positive serum type)	32	32	0	0	32	8–50	No excess in 21	All reduce
Tabes dorsalis (G P type)	10	2	8	10	0	12–40	In 9 no excess	All reduce
Tabes dorsalis (neg Wass type)	10	0	10	0	10	14–49	No excess in 5	All reduce
Acute infectious meningitis	14	8	6	0	14	94 up	Marked excess	No reduction
Tuberculous meningitis	6	2	4	0	6	*	Excess in 3	In 2 no reduction
Spinal cord tumors	4	0	4	0	4	0–18	Excess	Not all reduce

* Very many

distinctive features found in the cerebrospinal fluid In the Plaut type of cerebrospinal syphilis the Wassermann reaction is negative in the cerebrospinal fluid and positive in the serum The positive type of this disease consists of those cases which have a positive Wassermann reaction in both the serum and spinal fluid The occurrence of this type is common enough to demand a separate heading The serological types of tabes, as their names suggest, present features which could be utilized as therapeutic indices As has been pointed out before, there are cases of tabes which should not be subjected to antiluetic remedies [3] This type of tabes is shown under the heading of negative Wassermann type, in which both serum and spinal fluid are negative to the Wassermann test Whether, from a therapeutic standpoint, the general paresis type should be considered together with negative Wassermann type cannot be decided at present We have, however, data permitting the conclusion

3 Kaplan Jour Am Med Assn, 1910, lv, 1952

that the hyperlymphocytic type and the positive serum Wassermann type of tabes are suitable for therapeutic measures It is permissible to argue that in the hyperlymphocytic type we most likely have the serological expression of an exudative meningeal condition, an index of the active progression of the disease The tables of therapeutic results will show how these forms are influenced by therapy In speaking of a general paresis type of tabes we do not refer in any way to the clinical aspects of the disease, but only to the fact that in these cases there is a positive Wassermann reaction in the cerebrospinal fluid The positive serum type of tabes, in our experience comprises about 66 per cent of all cases [3]

In the cell-count of general paresis may be found the link that permits of the contention that some clinical varieties of initial so-called neurasthenoid paresis flow out of a preexisting cerebrospinal syphilis, or that the soil favorable for the development of paresis in some cases consists of tissue changes produced by syphilis of the brain and cord This view was expressed in a personal communication by Dr Charles L Dana, and is a theme worth investigating, as timely therapeutic measures may arrest the progress of the disease in this stage and prevent its becoming incurable The chief distinctive feature between cerebrospinal syphilis and general paresis is the high cell-count in the former As there are many instances in which the spinal fluid Wassermann is positive in lues cerebrospinalis, it seems to us that, serologically, the cell-count is alone reliable In the majority of instances the count in general paresis is seldom over seventy per c mm Although it is only a conjecture, it may nevertheless be advanced that the lowest cell-count in cerebrospinal lues may be the serological transition of this disease to general paresis If such a transition really exists, and if spinal fluid analyses could determine it, it becomes apparent how important these analyses will prove in the prophylaxis

In considering the infectious forms of meningitis, which are, as a rule, acute, pus may at times be encountered Although actual purulent fluids have not come to our notice while doing the above researches yet we have had cases in which the number of cells was so great that they could not be counted The reason why tuberculous meningitis is considered under a separate heading is that in this form of disease the fluid, as a rule, reduces Fehling's solution Only when the tuberculous process becomes complicated by another organism and large numbers of polynuclear cells appear in the fluid, does the reduction cease to manifest itself

The reduction may at times be absent in very active forms of cerebrospinal syphilis this phenomenon going parallel with an increase in the polynuclear elements One such case showed the presence of 100 polynuclear cells per c mm It will be pointed out later that as these cells

TABLE 3—POST-THERAPEUTIC FINDINGS

	Serum Wass	Cerebrospinal Fluid — Wass	Cells	Globulin	Fehling's Red
TABES DORSALIS					
Mr O—					
Before treatment	+	w+	90	Normal	Reduces
3 months after salvarsan	+	w+	68	Normal	Reduces
Mr P—					
Before treatment	—	—	33	Normal	Reduces
3 weeks after salvarsan	—	—	25	Normal	Reduces
8 weeks after salvarsan	—	—	12	Normal	Reduces
Mr D—					
Before treatment	+	—	95	Normal	Reduces
8 weeks after salvarsan	—	—	74	Normal	Reduces
12 weeks after salvarsan	—	—	51	Normal	Reduces
Mr M—					
Before treatment	+	—	31	Normal	Reduces
12 weeks after salvarsan	—	—	3	Normal	Reduces
CEREBROSPINAL LUES					
Mr D—					
Before treatment	w+	+	134	Excess	Reduces
10 days after salvarsan	—	—	60	Normal	Reduces
6 weeks after salvarsan	—	—	26	Normal	Reduces
Mr H—			*100		
Before treatment	+	+	†127	Excess	No reduction
After 7 weeks' Hg injections	+	+	*4	Slight excess	Reduces
			†73		
Mr H V—					
Before treatment	+	—	98	Slight excess	Reduces
8 weeks after salvarsan	+	—	91	Slight excess	Reduces
Mr Z—					
Before treatment	+	—	352	Excess	Reduces
After 7 weeks' Hg injections	+	—	52	Normal	Reduces
After 5 months' Hg injections	—	—	217	Normal	Reduces
Mr W—					
Before treatment	—	+	162	Slight excess	Reduces
2 weeks after salvarsan	—	+	35	Slight excess	Reduces
Mr Mc C—					
Before treatment	+	—	33	Excess	Reduces
3 weeks after salvarsan	—	—	14	Normal	Reduces
Mr T—					
Before treatment	+	—	253	Excess	Reduces
4 weeks after salvarsan	+	—	59	Excess	Reduces
Mr A—					
Before treatment	+	—	†357		
			*4	Excess	Reduces
1 week after salvarsan	+	—	309	Excess	Reduces
3 weeks after salvarsan	+	—	188	Excess	Reduces
9 weeks after second salvarsan	w+	—	95	Slight excess	Reduces
Mr P—					
Before treatment	+	—	121	Excess	Reduces
After 8 weeks' Hg inunctions	+	—	27	Normal	Reduces
Mr Do—			†267		
Before treatment	+	—	*67	Excess	Reduces
1 month after salvarsan	+	—	11	Normal	Reduces
Mr S—			†138	Excess	
Before treatment	—	—	*9		
1 week after salvarsan		—	80	Normal	Reduces
SUPPURATIVE MENINGITIS					
Mr Y			*42		
Before treatment	—	—	†160	Excess	No reduction
1 week after surgical treatment	—	—	*90		
			†96	Excess	Slight reduction
GENERAL PARESIS					
Mr Og—					
Before treatment	+	+	11	Excess	Reduces
5 weeks after salvarsan	+	+	11	Excess	Reduces
Mr Hu—					
Before treatment	—	—	13	Excess	Reduces
After 9 months' Hg injections	—	+	13	Normal	Reduces
M S—					
Before treatment	+	+	30	Excess	Reduces
1 month after salvarsan	+	+	17	Excess	Reduces

* Polynuclears † Lymphocytes

he presented absolute signs of cerebrospinal syphilis The same holds true in the case of Mr P, who at first presented serologically the signs of lues cerebrospinalis, but after eight weeks of mercury inunctions showed the neuroserological picture of tabes of the positive serum Wassermann type For the reappearance of the cells in the case of Mr Z we are not in a position to offer an explanation This is a young man who had a complète hemiplegia, undoubtedly due to a syphilitic thrombosis He has entirely recovered the use of his right side and there remains nothing of his original trouble but an increase of reflexes on the right side From the position of therapy the value of a contemporaneous study of clinical progress and serological behavior in a given case is self-evident In the case of Mr A it was the serological findings as well as the slight clinical improvement which prompted us to repeat the injection of salvarsan The clinical improvement in all our cases, however, did not always go hand in hand with the serological The changes in the serum and spinal fluid cannot at present be bound by strict classifications, for the same disease behaves frequently in different patients differently The very much to be desired results, clinical and serological, obtained in Mr M, must not be expected in every case Our results offer as little hope in paresis as does clinical experience According to Dr C L Dana, there are cases in the early stages of this disease, in which the pathological substratum is a preexisting cerebrospinal syphilis, which can be checked by treatment At present we do not believe that any one can say whether there are clinical and serological distinctions to aid us in the early detection of this disease As already mentioned, Marie believes that a negative Wassermann reaction in the cerebrospinal fluid marks the incipient stage of paresis, the reverse is true in the late stages, and in the full fledged forms the Wassermann reaction is present in both media We have arranged our material according to this idea with following results

1 Incipient Stage (Marie) · Wassermann reaction positive in the serum, negative in the spinal fluid, globulin in excess, cells, from five to eighty per c mm

Of our twelve cases of early paresis five corresponded with this theory and seven did not

2 Fully Developed Stage (Marie) Wassermann reaction positive in both media, globulin in excess, cells, from eight to seventy-eight per c mm

All of our cases of fully developed paresis corresponded perfectly

3 Stage of Paretic Decline (Marie) · Wassermann reaction negative in the serum, positive in the spinal fluid, globulin in excess, cells, from nine to forty-nine per c mm

We had nineteen cases of advanced paresis, thirteen of which agreed with this idea

It requires a very large number of cases to decide whether this classification is feasible, and hence we are not in a position to speak definitely about it One case of beginning general paresis showed the serological picture which Marie considers that of the late stage If work on these lines should show that such a view could be held, neurological serology will become indispensable To control this work by animal experiments is impossible We will have to be content with slower methods, and wait patiently for sufficient corroborative post-mortem material

This work is of value in that many clinical manifestations have distinctive diagnostic features in the neuroserological study The point not sufficiently emphasized is the difference between the acute and chronic meningitides In the acute forms, except the tuberculous, the Fehling reduction is always absent, violet color developing instead In the chronic forms of meningitis the Fehling reducing substance is present, provided only a few polynuclear cells are encountered As the purulent process subsides in the acute meningitis and the polynuclear elements disappear or diminish in the chronic forms, Fehling's reduction reappears This point is of interest as a gauge of progress in meningitis of any variety Such an improvement can be observed in the case of Mr H , in whom the reduction was absent while the polynuclear cells were numerous, and it promptly returned as these cells diminished in number The patient's clinical condition improved at the same time

SUMMARY

The above work allows of the following conclusions

1 There is a diagnostic and prognostic value to be derived from neuroserological studies

2 Negative cell-counts, as a rule, exclude diseases classified among the positive types and vice versa

3 The hyperlymphocytic and the positive serum Wassermann types of tabes are the ideal forms of this disease for successful treatment

4 It is permissible to argue that this hyperlymphocytosis is the expression of an exudative process

5 The presence of large numbers of polynuclear cells in the spinal fluid is significant of an acute meningitic process, be it luetic or due to any other cause

6 The diminution or the disappearance of the polynuclear cells is to be considered as a favorable prognostic sign

7 In a child with meningitis the presence of Fehling's reduction in the cerebrospinal fluid speaks strongly for the tuberculous nature of the meningitis

This article is in the nature of a preliminary report from the laboratory point of view, a more extensive work being in preparation by us together with Drs G H Kirby and M J Karpas of the staff of the Manhattan State Hospital, Ward's Island

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STUDIES IN BONE METABOLISM THE ETIOLOGY OF NON-PUERPERAL OSTEOMALACIA*

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The present investigation is a further contribution to the study of mineral metabolism and is designed to throw more light on the etiology and process in osteomalacia A correct interpretation of this process is of the greatest importance in an understanding of the metabolism of bone since the two views regarding the nature of the osteoid tissue in osteomalacia — the one that it is an old bone from which the mineral constituents have been dissolved out, and the other that it is new bone poor in mineral constituents — are based respectively on the two opposing views regarding the metabolism of bone — the one, that bone is dead tissue not undergoing metabolism, the other, that it does have a metabolism Anatomical investigations not having been successful in deciding between these two views, chemical methods were applied which led to the conclusion that bony tissue, like other tissue, is continuously being destroyed and replaced by new, and that osteomalacia is due to a disturbance of the balance whereby the new tissue is poor in calcium salts and therefore soft[1] A study of the etiology led to the conclusion that the starting point is an increased catabolism of bony tissue due to a need of calcium salts elsewhere and that the tendency of physiological activity to overproduction which is responsible for the production of antitoxins and acquired immunity is also an important factor in leading to the long-continued increased catabolism of calcium after the original need

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1 In view of these findings it is interesting to note that v Recklinghausen has recently been obliged to retract his interpretation of the *Gitterfiguren* which was largely responsible in upholding the opposing theory and to admit that it is not possible to differentiate morphologically between old bone from which the mineral salts have been removed and new bone poor in lime salts (von Recklinghausen Untersuchungen uber Rhachitis und Osteomalacie 1910 See especially chapter xiii and pages 343 and 346)

has ceased to exist.[2] The present investigation is the result of an excellent opportunity of studying a rare case of non-puerperal osteomalacia and was designed to test the above theory of the nature of the process, and to investigate the relation of the need of calcium salts and the tendency of overproduction to the etiology.

The following is an extract of her history and physical examination:[3]

CASE REPORT

History.—The patient, a woman aged 42 and unmarried, dates her illness to 1891 when she noted a hard painless nodule about the size of a bean on the right side of the lower jaw. Six months later the growth, which had by then increased to the size of a hen's egg, was removed together with a piece of the jaw. In 1895 she began to suffer from loss of appetite, vomiting, obstinate constipation and severe neuralgia in the face and upper jaw and began to walk with difficulty. She noticed that her ankles would "bend in and out" on walking "as if they were made of rubber." Then a gradual stiffening of the back and stiffness and creaking of the knees developed so that after five months she could get about only with the greatest difficulty. In the fall of this year small hard painless nodules were noticed on her shin bones. The largest on the left was about the size of a walnut. In 1897 she was forced to give up work entirely. A year later while riding a low tricycle she fell and fractured the right thigh. This fracture, which she describes as causing her surprisingly little pain, laid her up seven weeks, after which and until ten weeks ago she was able to move about by leaning on a chair. While laid up she had an attack of renal colic, i. e., intense colicky pain radiating downward from her right kidney region. Three weeks later she passed several small

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2. McCrudden, Chemical Analysis of Bone from a Case of Human Adolescent Osteomalacia, Journ. Biol. Chem., 1910, viii, 199. The Composition of Bone in Osteomalacia, Am. Journ. Physiol., 1906, xvii, 32. A Study of the Metabolism in Osteomalacia, Am. Journ. Physiol., 1905, xiv, 211. The Effect of Castration on the Metabolism, Journ. Biol. Chem., 1910, viii, 185. The Effect of Castration on the Metabolism in Osteomalacia, Am. Journ. Physiol., 1906, xvii, 211. Studies of Bone Metabolism, Especially the Pathological Process, Etiology and Treatment of Osteomalacia, THE ARCHIVES INT. MED., 1910, v, 596.

The gynecologists are at present inclined to the hypothesis that osteomalacia is a disease of the adrenals. The original basis for this hypothesis was the experience of Bossi, an Italian physician, who on Dec. 16, 1906, and on four successive days administered epinephrin in a case of osteomalacia. At the end of that time the patient had much less pain and was therefore discharged as cured. *Within four weeks of the first treatment* the journal containing publication of the results appeared. (Bossi, Nebennieren und Osteomalakie, Centralbl. f. Gynak., Jan. 19, 1907, No. 31, p. 69.) A number of other just such experiments have since been reported in the literature. In all cases "cure" was reported soon after treatment and meant simply relief from pain. The rapidity with which tenderness and pain disappear at times even without treatment in osteomalacia, is well known and does not indicate a cure of the disease. The case reported by Kaessman (Ein Beitrag zur Adrenalin Behandlung des Osteomalakie nach Bossi, Centralbl. f. Gynak., 1907, xxxi, 1376) may be typical of what happens to some of these patients. Kaessman administered epinephrin daily from Sept. 6 to Sept. 11, 1907, and on September 14 sent the patient away better but with instructions to keep up the treatment. Nine days later, on September 23, the patient returned worse than ever. The suprarenal theory does not seem worthy of very serious consideration.

3. She was under the direct care of Dr. Henry K. Marks of this hospital.

gray stones These attacks of pain recurred, at intervals of six to eight months Usually, about three weeks after each attack, she would pass a stone about the size of a pea Since May, 1904, she has had no attacks Between 1900 and 1905

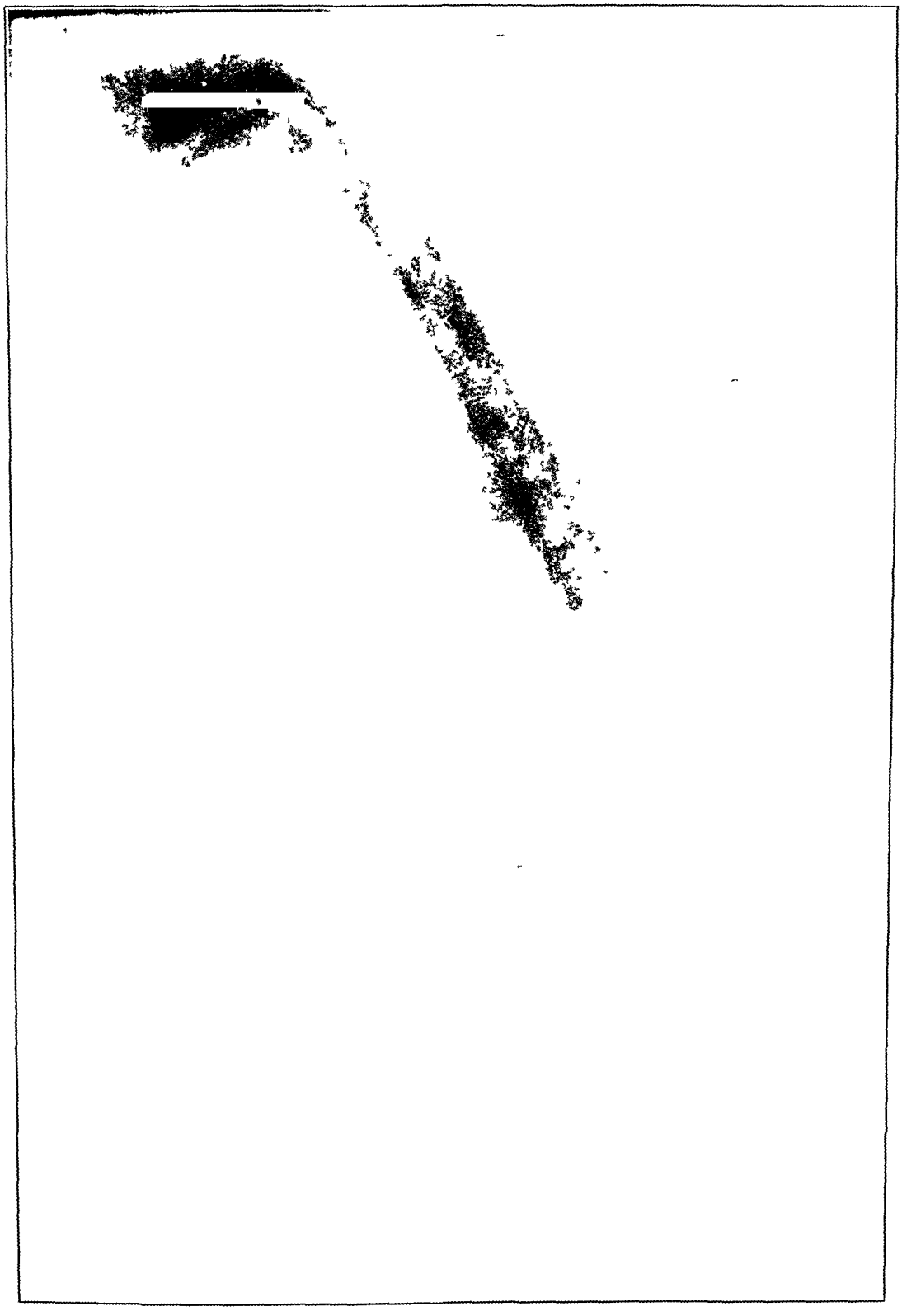

Fig 1 —X-ray plate showing bony tumor from the left shin of a patient suffering from osteomalacia

her symptoms did not progress Then the stiffness of her knees and back increased and she noticed a painless enlargement near the lower edge of the spine In 1907

she began to grow deaf in the right ear A year later there was difficulty in breathing following the appearance of a bony growth in the right nostril In the spring of 1909 it was noticed that her left eyeball protruded and she complained of dimness of vision and seeing double There was no pain In 1909 small nodules were noticed on her forehead About this time she fractured the second metacarpal bone of the right hand by shaking hands with a friend In August 1910,

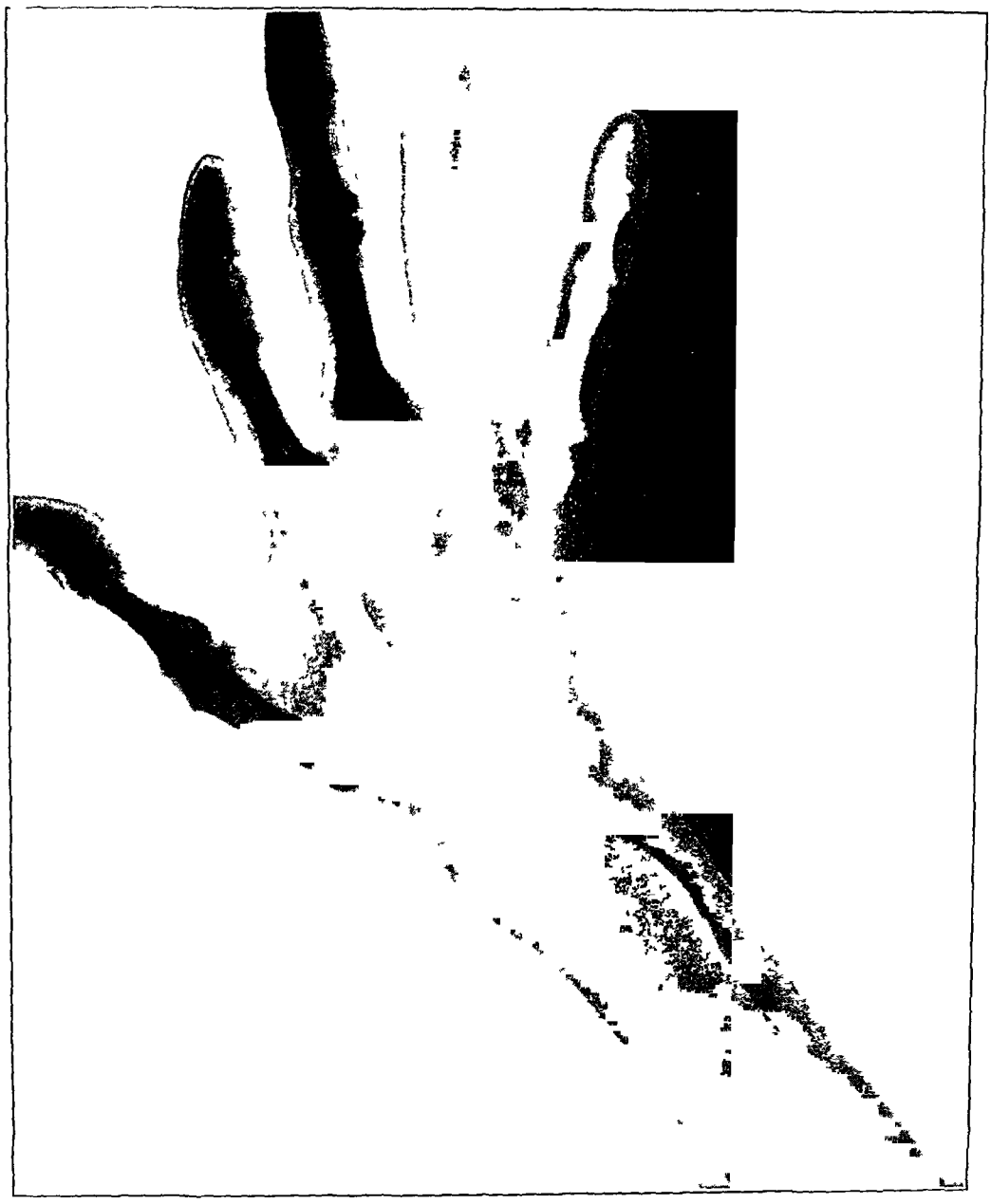

Fig 2—Rarefaction in the second phalange of the index and third fingers and in the fifth metacarpal bone of patient with osteomalacia

while washing her hands she dislocated the terminal phalanx of the left index finger For the last ten weeks she has been bedridden on account of increasing stiffness and weakness She feels no pain on lying still but only on movement or when handled

Physical Examination of the Osseous System—The patient is a poorly nourished, emaciated, distorted, middle-aged woman She lies comfortably in bed except when she attempts to move A slight ridge can be felt extending along the sutural lines of the skull There is a hard nodule about the size of a pea on the temporal bone behind the right ear, an indefinite firm swelling behind the left ear, and three small firm nodules on the frontal bone The nodules are not tender and not movable There are two firm swellings on either side of the raphé between the hard and soft palate There is a sharp bony exostosis on the outer edge of the outer third of the right clavicle There is a marked rosary The right costal margin is somewhat depressed At the left over the costochondral margin there is an elevation which is tender There is moderate kyphosis of cervical and upper dorsal vertebræ and marked scoliosis The sacrum is very prominent The iliac wings are thickened and nodular The absence of about an inch of the lower jaw gives the face an asymmetrical appearance The legs are emaciated The left leg is somewhat longer than the right, owing to bowing out of the right femur just above the middle (site of the old fracture, over which is a large callus) The surfaces of both shins are roughened Just below the middle of the left tibia, and involving chiefly the inner surface, is a hard, oval, bone like mass 11 cm long, and 13 cm wide It is not tender or movable and the skin is not adherent On the second metacarpal joints of both hands, there are hard swellings The terminal phalanx of the left index-finger is movable laterally

X-Ray Pictures—Examples of the bony tumors and bone rarefactions are seen in Figures 1 and 2 respectively Figure 1 shows a tumor from the left shin In Figure 2 examples of rarefaction may be seen in the second phalanges of the index finger and third finger and in the fifth metacarpal bone

Briefly summarized, the condition is one of osteomalacia following the appearance of multiple bony tumors

EXPERIMENTAL DATA

A complete metabolism experiment of ten days' duration, in which the intake and outgo of nitrogen, calcium, magnesium, sulphur and phosphorus was determined, was carried out The diet consisted of the mixed diet of the hospital, only foods that were not homogeneous enough to sample properly being excluded The diet for a week preceding the experiment was the same as that used in the experiment, so that there was no abrupt change The details of feeding, collecting excreta, sampling and analyzing have been described in earlier papers[2] The diet follows

NOVEMBER 17—*Breakfast* White bread, 51 8 gm oatmeal, 104 4 gm, scrambled eggs 32 9 gm, coffee 400 cc, milk 4300 cc, water, 200 0 cc *Luncheon* Potatoes 51 2 gm, rice 98 5 gm ham, 23 1 gm, custard 112 4 gm, milk, 205 0 cc, chicken broth 160 0 cc, water, 200 0 cc At 3 30 p m milk, 250 0 cc *Supper* Hamburg steak 34 2 gm sweet potatoes, 23 6 gm, banana 44 gm, milk, 130 0 cc, water, 228 0 cc

NOVEMBER 18—*Breakfast* Graham bread and butter from stock oatmeal 96 4 gm, lamb chop meat 14 6 gm coffee, 500 cc, milk, 470 0 cc water 360 0 cc water (injection*), 300 0 cc *Luncheon* Bread and butter from stock chicken meat 23 3 gm spinach, 29 7 gm, rice 41 4 gm water 250 0 cc chicken

*It was occasionally necessary to give an enema to move the bowels Tap water was used and the amount used added to the food to be analyzed

broth, 1600 c c milk 1500 c c *Supper* Bread and butter from stock, meat, 265 gm junket, 1146 gm chicken broth, 1000 c c milk, 1500 c c, water, 4500 c c

NOVEMBER 19—*Breakfast* Oatmeal 850 gm sausage, 330 gm water, 2000 c c, coffee 600 c c milk, 1000 c c *Luncheon* Chicken, 259 gm, rice, 792 gm, custard 481 gm Graham bread and butter from stock water, 2100 c c, milk 2100 c c, soup, 1700 c c, gravy 500 c c *Middle afternoon* milk, 2500 c c, water, 3906 c c *Supper* Meat 239 gm, banana 403 gm, water 1500 c c milk 2000 c c soup, 1600 c c

NOVEMBER 20—*Breakfast* Oatmeal, 932 gm eggs, 406 gm, brown bread and butter from stock, water 2000 c c coffee 1400 c c, milk, 3550 c c water (injection) 2100 c c *Luncheon* Brown bread and butter from stock, chicken 469 gm, rice, 638 gm spinach 463 gm ice cream 410 gm, soup 135 c c, water, 2000 c c, milk 2506 c c *Supper* Brown bread and butter from stock, soup 1700 c c milk 5000 c c water 2000 c c

NOVEMBER 21—*Breakfast* Brown bread and butter from stock, oatmeal 971 gm, water 2000 c c, milk, 2500 c c coffee 700 c c *Luncheon* Beefsteak, 257 gm, rice 713 gm, apple sauce 1123 gm, bread and butter from stock, water 2000 c c milk 4000 c c soup 1700 c c *Supper* milk 1850 c c, oyster soup, 1700 c c water 2000 c c

NOVEMBER 22—*Breakfast* Banana 374 gm, oatmeal 885 gm water, 1800 c c, milk 3500 c c, coffee, 700 c c water (injection) 3150 c c *Luncheon* Chicken, 330 gm, rice, 760 gm, custard 938 gm, bread and butter from stock, water 1800 c c soup 1800 c c milk 2500 c c *Supper* Meat 218 gm, sweet potato 517 gm, water 2000 c c, milk 470 c c broth, 150 c c

NOVEMBER 23—*Breakfast* Bread and butter from stock, oatmeal, 911 gm, egg milk sherry mixture, 2150 c c, water 1200 c c coffee, 700 c c, milk, 3500 c c *Luncheon* Bread and butter from stock, rice 911 gm custard, 931 gm, chicken, 322 gm, water, 2000 c c, soup, 1700 c c, milk, 2500 c c, gravy, 250 c c *Supper* Water, 2000 c c egg milk sherry, 2350 c c, soup, 1700 c c

NOVEMBER 24—*Breakfast* Bread and butter from stock, banana, 427 gm, water 2200 c c, sausage 494 gm, coffee 700 c c, milk, 1000 c c *Luncheon* Rice, 880 gm, peas, 523 gm, turkey, 415 gm, milk, 225 0 c c, water, 2100 c c, broth, 1800 c c *During afternoon* milk, 2500 c c *Supper* Chicken, 243 gm, apple sauce, 767 gm, milk, 4700 c c, broth, 800 c c, water, 2100 c c

NOVEMBER 25—*Breakfast* Banana 428 gm, oatmeal, 946 gm, water 2100 c c, milk, 5100 c c, coffee 700 c c *Luncheon* Rice, 478 gm, spinach, 438 gm, chicken, 331 gm, water, 2100 c c, broth, 1700 c c, milk, 2500 c c, gravy, 550 c c *During morning* Milk, 250 c c *Supper* Bread, 164 gm, lamb, 238 gm, peaches, 640 gm, egg milk sherry mixture, 2300 c c, milk, 4700 c c, water 2300 c c, broth, 1600 c c

NOVEMBER 26—*Breakfast* Bread, 397 gm, oatmeal, 670 gm, beefsteak, 285 gm, milk, 4200 c c, water, 1000 c c, coffee, 700 c c *Luncheon* White sauce, 400 gm, apple sauce, 682 gm, bread, 256 gm, water, 2000 c c, milk, 2250 c c, soup, 1600 c c *During day* Water, 2000 c c

For the whole experiment Graham bread 5366 gm, white bread, 2134 gm, butter, 6125 gm, salt 59 gm

We neglected to weigh the patient at the end of the experiment, but she appeared to be steadily gaining in weight and strength and there was a considerable retention of nitrogen

The accompanying tables give the results

TABLE 1—METHODS OF ANALYSIS AND AMOUNTS USED

	Amounts Used for Analysis			Method of Analysis
	Urine c c	Food* gm	Feces† gm	
N	5	1	1	Kjeldahl
CaO	200	10	1	McCrudden[4]
MgO	200	10	1	McCrudden[4]
S	50	2	2	Folin[5]
P_2O_5	50	2	1	Neumann[6]

* Total weight 3104 7 gm † Total weight 246 7 gm

TABLE 2—ANALYSIS OF URINE DAY BY DAY*

Day	N gm	CaO gm	MgO gm	S gm	P_2O_5 gm
1	8 08	0 291	0 106	0 590	1 692
2	8 40	0 293	0 119	0 648	1 680
3	10 28	0 333	0 139	0 734	1 840
4	10 08	0 379	0 107	0 716	2 020
5	9 56	0 315	0 123	0 656	1 948
6	10 56	0 350	0 131	0 730	1 880
7	10 92	0 330	0 129	0 804	2 072
8	11 52	0 298	0 129	0 762	1 996
9	10 76	0 477	0 045	0 788	2 048
10	9 52	0 278	0 123	0 684	1 936
Total	99 68	3 344	1 151	7 112	19 112

* The urine analyses were made in duplicate

TABLE 3—COMPARISON OF ANALYSES OF URINE, FOOD AND FECES*

	N gm	CaO gm	MgO gm	S gm	P_2O_5 gm
Urine total	99 68	3 344	1 151	7 112	19 112
Feces total	11 72	18 80	3 40	1 024	15 57
Total outgo	111 4	22 14	4 55	8 14	34 68
Total intake (food)	121 4	21 17	4 69	10 03	35 55
Retention	10 0		0 14	1 89	0 87
Loss		0 97			
Per cent retained	+8 3%	—4 6%	+3 0%	+18 8%	+2 4%

* The food and feces analyses were made in triplicate

DISCUSSION

For a correct interpretation of the figures, the percentage accuracy of the results should be known It is not necessary to give the weights of all the final precipitates with a discussion of the accuracy of each since the approximate accuracy of the methods can be judged by anyone familiar with them The last figures in each case in the reported balances are probably correct to within a few figures—that is the retention of nitrogen lies between 9 98 and 10 02 gm , the loss of calcium oxid between 0 93 and 1 01 gm , etc[7]

4 McCrudden F The Quantitative Separation of Calcium and Magnesium, etc Jour Biol Chem 1910 vii 83

5 Folin, O Sulphate and Sulphur Determinations Jour Biol Chem 1905, i 131

6 Neumann A Einfache Veraschungs Methode etc Ztschr f physiol Chem 1902 xxxvii 131, Nachtrage zur Simultangemisch Veraschung Ztschr f physiol Chem 1904 xlii 35

7 The probable limits of experimental error are about as follows

	N	S	CaO	MgO	P_2O_5
Total urine	±0 2	±0 03	±0 01	±0 01	±0 05
Feces	±0 02	±0 01	±0 03	±0 02	±0 07

Taking the larger of these two sets as the possible error for the total outgo we get

Total outgo	±0 2	±0 03	±0 03	±0 02	±0 07

For food the figures are about as follows

Food	±0 2	±0 05	±0 04	±0 02	±0 07

Taking the larger of each of these two sets for the error in the balance we get

Balance	±0 2	±0 05	±0 04	±0 02	±0 07

It is plain that there was a definite loss of calcium accompanied by a retention of all other elements and that the amounts lost and retained were outside the limits of experimental error The question arises Is the amount lost a significant amount? The significance of the loss depends partly on the amount metabolized, partly on the relative loss of other substances The amount of calcium oxid lost in twelve days was about 1 0 gm , nearly 5 per cent of the amount in the food and over three times the average daily amount in the urine, and is probably lost chiefly through the urine for the amount in the urine is nearly double the normal [8] Furthermore everything else was being retained, the retention running from 3 per cent in the case of magnesium to 19 per cent in the case of sulphur These relations cannot be normal Towle[9] has pointed out that there is a parallelism in the metabolism of nitrogen and calcium in health and in disease unless very large quantities of calcium are especially given And this has been found to be true for other elements The balance given in Table 4 was found in the case of a healthy boy

TABLE 4 —METABOLISM OF A HEALTHY BOY

	N	S	CaO	MgO
Total intake	86 10	6 138	14 99	3 26
Total outgo	71 46	5 222	12 42	2 53
Balance	+14 64	+ 916	+ 2 57	+ 0 73
Per cent	+17 0	+14 9	+17 1	+22 4

The results of Hoffstrom,[10] who studied the metabolism of a pregnant woman for a long period, showed similar parallelism in retention between nitrogen and mineral salts

The retention of sulphur and magnesium is greater in proportion than that of nitrogen and corresponds to a growth of tissue richer in sulphur and magnesium than any of the soft tissues — such a tissue as bone This condition is in accord with McCrudden's conception regarding the process going on, namely, that bony tissue is being catabolized and that the new bone laid down to replace it is poorer in calcium

8 The loss of calcium and retention of magnesium and sulphur are not so great in this experiment as in the experiment on which my conception of the etiology and process was based In one of those experiments there was an average daily loss of nearly 1 gm of CaO (Am Jour Physiol , 1906, xvii, 211), and Berger (Presse méd , 1905, xiii, 249), speaks of a case in which he analyzed the urine only and found 0 0 gm CaO per day The patient was in relatively good condition at the time of the present investigation, probably as a result of the good hygienic environment If we could have studied her condition when the process was more active, greater losses might have been expected

9 Towle C Calcium Metabolism with Special Reference to Exophthalmic Goiter Am Jour Med Sc , 1910 cxl, 100

10 Hoffstrom K Eine Stoffwechseluntersuchung während der Schwangerschaft, Skandin Arch f Physiol , 1910, xxiii, 326

but richer in sulphur and magnesium than normal bone, similar to osteoid tissue plus magnesium salts.

The clinical course of this case of osteomalacia is in accord with McCrudden's conception of the etiology The various bony tumors need lime salts for their growth and, as already pointed out in earlier papers, the bones act as a reservoir of lime salts from which the body may draw in time of need [11]

The tendency of the body to overproduction, to the continuation of an activity once started after the need for activity has ceased to exist, is shown in this case The hard tumors which were probably responsible for starting the increased catabolism of bone were no longer actively and rapidly growing, yet the flux of calcium salts from the bones continued and, as shown by the metabolism experiment, the calcium was simply excreted There are many analogies for this process. Under the name of "functional inertia," Harris[12] points out that it is as fundamental and important an attribute of living matter as irritability itself He defines functional inertia as "that property of protoplasm whereby living matter contrives to remain in a functional *status quo ante* notwithstanding that it has received a stimulus, or, having responded to the stimulus, it contrives to exhibit its functional activity for a certain time after the stimulus as a form of energy has ceased" The condition may be compared with that of a heavy door which, when at rest, requires a certain time to get into full swing after it has been pushed and, when moving, takes time to stop if held Of examples of latent period in starting activity, there is the latent period of muscular contraction, that occurring after glands are stimulated through their nerves and before they begin to secrete, and that occurring before the heart-beat begins to accelerate its rate when the augmentor or accelerator nerves are stimulated Of examples of continued activity after the original stimulus has ceased

11 Further evidence to this effect has recently appeared King, Bigelow, and Pearce (Experimental Obstructive Jaundice, Jour Exper Med, 1911, xiv, 148) have shown that the calcium content of the bones decreases in cases of obstructive jaundice in which calcium is needed to neutralize the toxic effects of the bile acids Schmidt (Verhandl d deutsch path Gesellsch, 1909, xiii, 3) has pointed out that the decrease of calcium in the bony system in rickets is accompanied by an increase of this element in the soft tissues such as muscle and liver, and Higbee and Ellis, in a recent paper on osteitis deformans (Jour med Research, 1911, xxiv, 43)—a condition which is recognized as one of localized osteomalacia—state that calcification of the arteries is so common in these cases that it has been mentioned as a possible etiological factor.

Dr Charles F Painter of Boston has called McCrudden's attention to the occurrence of a late variety of non-rachitic bow-legs occurring in children about the time the epiphyses begin to harden Is it not possible that a flux of calcium might be started by the demand for this element by the hardening epiphyses analogous, in a way, to the physiologic osteomalacia noted by Hanau and Wild in the pelvic bones of pregnant women?

12 Harris, D The Functional Inertia of Living Matter, London, 1908

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may be mentioned the continuation of accelerated heart action for a time after stimulation of the augmentor nervous apparatus has ceased, the continued overproduction of free receptors which, according to Ehrlich's theory, is the explanation of acquired immunity and the overproduction which Weigert has pointed out is characteristic of all tissue repair These examples are analogous to the continued catabolism of the lime salts of bone after the original stimulus for this process has ceased [13] It is not improbable that overproduction may be another example of the factors of safety with which as Meltzer[14] has pointed out, the body is so well endowed

The recurrence of attacks of osteomalacia earlier and earlier in succeeding pregnancies, and the increasing severity of subsequent attacks, make one think of the more severe and rapid production of symptoms of certain diseases e g, serum disease and others after a previous inoculation — a kind of allergy,[15] or, to put it still more broadly, "a cell stimulated to perform a certain act not only continues to perform that act for some little time after the stimulus has ceased, but, what is more, on a second occasion a slighter stimulus will induce the like series [16]

It ought to be emphasized that the conception regarding the etiology and process in osteomalacia outlined here is, of course, based *not on these theories* of functional inertia and allergy, *but on the facts* observed in chemical clinical and anatomical investigations The analogies are cited merely to show that, in all probability, the process in osteomalacia is but a special example of certain more general laws governing the *modus operandi* of living matter

SUMMARY

The findings in the present case of osteomalacia are, then, in accord with the views outlined in this and previous papers[2] regarding the process and etiology of osteomalacia and give further support to these views The loss of calcium and retention of magnesium and sulphur are in accord with the conception of the process in osteomalacia, as one in which the bone is undergoing metabolism but in which the new bone laid down is an osteoid tissue poor in lime salts but richer than normally in magnesium The presence of bony tumors preceding the osteomalacia is in accord with the conception that the starting point in osteomalacia can

13 It is not improbable that another example of such overproduction or functional inertia is the change in the metabolism brought about by morphinism which enables the body to destroy increasing amounts of morphin but which continues and has a damaging effect on the organism itself if the drug is suddenly withdrawn

14 Meltzer, S J The Factors of Safety in the Animal Structure and Economy, Harvey Society Lectures, 1906-1907

15 v Pirquet, C Allergy, THE ARCHIVES INT MED, 1911, vii, 259 and 382

16 Adami The Principle of Pathology, 1910, i, 195

usually, if not always, be traced to a demand for calcium salts And the continued excretion of an excess of calcium when the bones really need this element is in accord with the conception regarding the importance of overproduction in bringing about the softening of the bone

Sixty-Sixth Street and Avenue A

THE PHTHALEIN TEST

AN EXPERIMENTAL AND CLINICAL STUDY OF PHENOLSULPHONEPHTHALEIN IN RELATION TO RENAL FUNCTION IN HEALTH AND DISEASE

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BALTIMORE

Phenolsulphonephthalein, which was first described by Remsen,[1] is a bright red crystalline powder, somewhat soluble in water and alcohol and readily soluble in the presence of alkalies The drug, as determined by Abel and Rowntree,[2] is *non-toxic, non-irritant* locally, and is excreted practically entirely by the kidneys and with extraordinary rapidity, appearing in the urine normally within a few minutes of injection In alkaline solution it presents a brilliant red color which is ideally adapted for quantitative colorimetric estimation

TECHNIC

In our earliest work only the time of appearance, the time of maximum intensity of excretion, and the time of gross elimination were considered In the course of the work it became evident that the color properties of this substance make it peculiarly well adapted for colorimetric methods of estimation, and for this purpose the Duboscq colorimeter was employed and has proved of the greatest value

In order to obtain data of real value it is essential to any functional test to know, not only the time of appearance of the drug in the urine, but exactly what part of the drug, a known amount of which has been administered, is recovered in a definite period of time

Twenty minutes to half an hour before administering the test, the patient is given 200 to 400 c c of water in order to insure free urinary secretion, otherwise delayed time of appearance may be due to lack of secretion

Under aseptic precautions a catheter is introduced into the bladder and the bladder completely emptied Noting the time, 1 c c of a carefully prepared solution[3] of the phenolsulphonephthalein containing 6 mg

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*From the Pharmacological Laboratory of the Johns Hopkins University and the Genito-Urinary and Medical Clinics of the Johns Hopkins Hospital

1 Remsen Am Chem Jour, 1884, vi, 280

2 Abel and Rowntree Jour Pharm and Exper Therap, 1909, i, 231

3 This solution is obtained as follows 0 6 gm of phenolsulphonephthalein and 0 84 c c of double normal sodium hydroxid solution are diluted with 0 75 per cent sodium chlorid solution up to 100 c c This gives the mono-sodium or acid salt, which is red in color and which is slightly irritant locally when injected It is necessary, therefore, to add 0 15 c c more of the twice normal hydroxid, a quantity sufficient to change the color to a beautiful Bordeaux red This preparation is non-irritant

to the c c is accurately administered subcutaneously, intramuscularly or intravenously by means of an accurately graduated syringe [4]

The urine is allowed to drain into a test-tube in which has been placed a drop of 25 per cent sodium hydroxid solution and the time of the appearance of the first faint pinkish tinge is noted

In patients without urinary obstruction the catheter is withdrawn at the time of the appearance of the drug in the urine, and the patient is instructed to void into a receptacle at the end of one hour and into a second receptacle at the end of the second hour

A rough estimate of the time of appearance can be made by having the patient void urine at frequent intervals without the use of the catheter In prostate cases it is wise to have the catheter in place until the end of the observation The catheter is corked at the time of the appearance of the drug in the urine and the cork is removed at the end of the first hour and at the end of the second hour, the bladder being thoroughly drained each time On many of the patients of this type on whom our observations have been made, a retention catheter has been in use as part of the routine treatment on account of the residual urine When a catheter is to be employed it is well previously to have the patient under the influence of hexamethylenamin

Each sample of urine is measured and the specific gravity taken Sufficient sodium hydroxid (25 per cent) is added to make the urine decidedly alkaline in order to elicit the maximum color The color displayed in the acid urine is yellow or orange, and this immediately gives place to a brilliant purple-red color when the solution becomes alkaline This solution is now placed in a liter measuring-flask and distilled water added to make accurately 1 liter The solution is then thoroughly mixed and a small filtered portion taken to compare with the standard, which is used for all of these estimations

In our earlier work the amount of drug excreted was estimated by means of the Duboscq colorimeter, the technic of which has been described in our original publication *

Recently the Autenrieth-Konigsberger colorimeter[5] has been modified by us and utilized for the quantitative estimation of phthalein A standard alkaline solution, 6 mg of phthalein to the liter, is placed in the wedge-shaped cup The urine, collected as for the other method, is diluted to a liter and a small filtered portion poured into the rectangular cup The wedge-shaped cup is now manipulated by means of the screw until the two sides of color field are identical in intensity The percentage is now read directly by the position of the indicator on the scale

4 We have used the Record 2 c c syringe which is graduated in fifths of a c c

5 This instrument is manufactured by Hellige in Freiberg, our modification can be obtained from Hynson and Westcott Baltimore Md

*Jour Pharm and Exper Therap 1909

This instrument is well adapted for the purpose, is approximately accurate, and is much cheaper than the Duboscq colorimeter

Fairly accurate estimations, however, can be obtained by means of graduated cylinders—equal quantities of the standard solution and the diluted urine being used in separate cylinders and the denser solution being diluted until the colors become identical The amount of drug in the solution being known, the amount in the urine can be readily calculated

When the collected urine has been made strongly alkaline it is necessary to estimate the phthalein within a few hours as the red color fades gradually under these conditions When it is desirable or necessary to defer the estimation for some hours or days, it is better to make the urine distinctly acid, under which condition the phthalein remains unchanged It should of course be made alkaline again when the estimation is made

The method heretofore utilized in connection with other tests, of determining the time necessary for total elimination, is erroneous for the following reason Whereas in the case of phthalein, a normal kidney excretes the greater part of the dye injected within two hours of the time of its administration, and then only a small trace for the next two hours, the moderately diseased kidney secretes a fair amount within the first two hours, say 50 per cent of that excreted by the normal kidney, but the concentration in the blood still being high it continues to excrete a fair amount in the following two hours, so that at the end of four hours little difference may exist in the total work accomplished One-hour and at most two-hour observations are therefore recommended In cases in which only slight changes in function exist this can be most accurately demonstrated by one-hour collection following the use of an intramuscular (lumbar) injection

THE INFLUENCE OF THE RÔLE OF ABSORPTION ON THE RATE OF EXCRETION

It must be admitted that a factor other than renal excretion, viz, absorption, enters in consideration in connection with the test when the phthalein is administered subcutaneously or intramuscularly Obviously, a considerable error is introduced from the standpoint of absorption in the use of the subcutaneous method, when factors, such as edema, which may modify the rate of absorption, exist On this account the excretion in health following different methods of administration has been studied in some detail

INTRAMUSCULAR AND SUBCUTANEOUS ABSORPTION OF SULPHONEPHTHALEIN

Meltzer and Auer[6] were the first to demonstrate that absorption from the intramuscular tissue is much more rapid than that from the subcuta-

6 Meltzer and Auer Jour Exper Med, 1905, vii, 59

neous tissues They worked with epinephrin, curare, fluorescin and morphin, and demonstrated beyond doubt that these substances found their way into the general circulation much more rapidly when the injections are made into the muscles Patta[7] was unable to detect any rise of blood-pressure following the intramuscular injection of epinephrin and concluded that the results obtained by Meltzer and Auer[6] were in reality due to intravenous injections Wallace,[8] working with epinephrin, obtained results identical with those of Meltzer and Auer, but also felt that the results were dependent on tearing of the veins and were in reality intravenous injections Joseph and Meltzer,[9] in their work in relation to physostigmin in poisoning by magnesia salts, again demonstrated intramuscular absorption to be far superior to subcutaneous Auer and Meltzer,[10] by methods used with specific intention of detecting whether the rapidity of intramuscular absorption was dependent on the tearing of veins during the injections or to the direct insertion of the needle into a muscle vein, proved satisfactorily that such accidents were not responsible for the rapidity of absorption, but that rapid absorption occurs through the walls of the blood-vessels of the muscles In the same communication they also asserted that absorption from the lumbar is much superior to that from the gluteal muscles

Phenolsulphonephthalein, by virtue of the properties whereby it is rapidly and quantitatively excreted by the kidney, furnished an excellent method of studying this problem An investigation into the comparative quantitative excretion of phenolsulphonephthalein following these two methods of administration was consequently undertaken

The first experiments were carried out on bitches The time of appearance of the drug in the urine following subcutaneous administration of 1 c c of phthalein solution (6 mg) and the quantitative output of phthalein for periods of varying lengths were determined The lumbar muscles of these dogs were then exposed by a small incision, direct intramuscular injection made, and the time of appearance of the drug in the urine and the quantitative output for corresponding periods again determined Finally, intravenous injections were given and similar observations were again made

The time of appearance was determined as follows A catheter was passed into the bladder and then 1 c c of sulphonephthalein was injected subcutaneously, intramuscularly or intravenously The bladder was then injected at 30-second and one-minute intervals with small quantities of warm sterile boric solution and this was immediately drained into flasks

7 Patta Arch ital de biol , 1906 xlvi 463
8 Wallace Med Rec , 1907 lxxi, 876
9 Joseph and Meltzer Jour Pharm and Exper Therap 1909, i, 369
10 Auer and Meltzer Jour Exper Med 1911, xiii, 328

containing a few drops of sodium hydroxid The first appearance of phthalein in the washings was noted and the amount of drug excreted for the varying periods was then determined

The results obtained from these observations appear in Table 1, from a study of which it will be seen that the time before appearance is shortest for the intravenous and that the drug appears much more rapidly (3 5 to 7 min) following an intramuscular than following a subcutaneous injection (5 5 to 12 minutes) The amount of excretion is dependent on the amount of absorption, the kidney function not playing a rôle inasmuch as the same dogs were used throughout for these

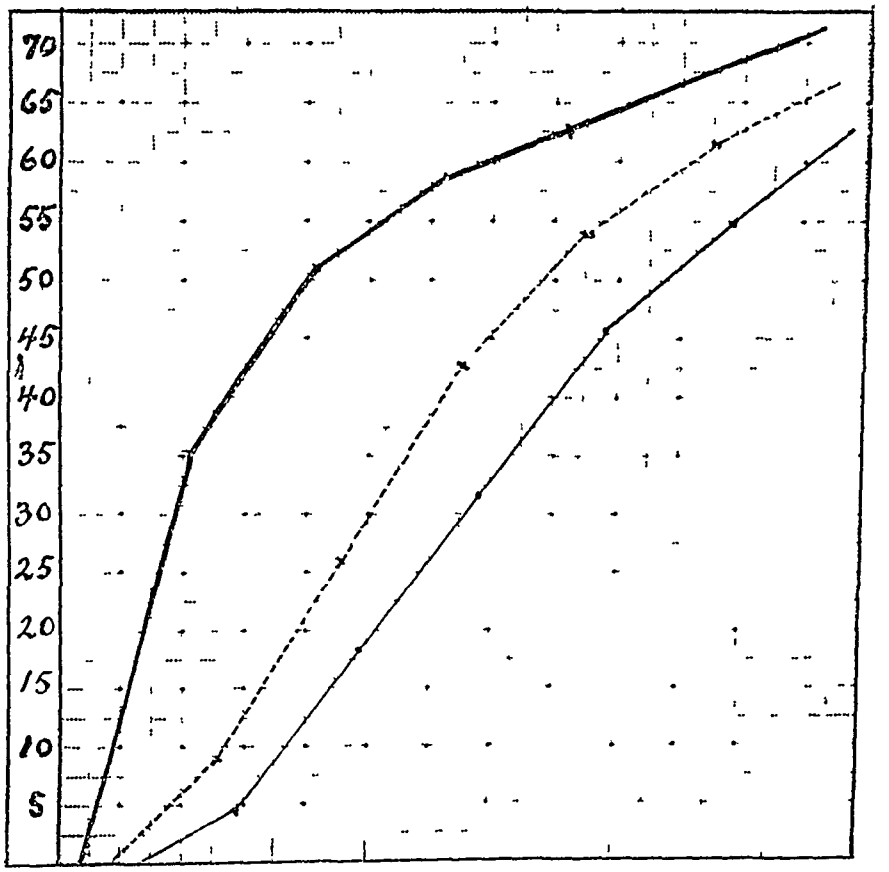

Chart 1 —Curve of excretion in a dog for one hour, estimations being made at ten-minute intervals • Upper black line represents the excretion after intravenous, the dotted line after intramuscular (lumbar) and lower black line after the subcutaneous administration

experiments, the kidney function being therefore approximately the same It appears that the absorption for one hour from the subcutaneous tissues averages from 5 to 10 per cent less than that from the intramuscular, while at the same time considerable variation (37 to 62 8 per cent) exists in the absorption for the same dog (Dog 5, Table 1) The absorption from the intramuscular tissue for one hour appears to display less variation (58 8-68 per cent), but the absorption is not absolutely complete, as

the excretion for one hour is somewhat less than that following intravenous injections

The difference, however, in the absorption from these two methods of administration is much more striking when one-half hour observations are taken—over twice as much absorption following intramuscular injections as compared with subcutaneous (Dogs 4 and 5, Table 1) This suggested to us the idea of the necessity of comparing the curve of excretion in order to obtain the real difference in the rate of absorption Estimations were made at ten-minute intervals following injections by all three methods of administration A comparison of the excretion in one dog (No 5, Table 1) is indicated in Chart 1 A similar comparison for the excretion in man following intravenous, lumbar, gluteal and subcutaneous administration is shown in Chart 2

TABLE 1.—COMPARISON OF EXCRETION OF PHTHALEIN IN DOGS FOLLOWING INTRAVENOUS, INTRAMUSCULAR (LUMBAR), AND SUBCUTANEOUS ADMINISTRATION

	Time of Appearance			Amount 1st ½ Hour			Amount 1 Hour		
	Subcut	Intramus	Intraven	Subcut	Intramus	Intraven	Subcut	Intramus	Intraven
Dog 1		5	1½			54 9	57 4	66 7	
		5	2			54 6	65	58 5	62 5
		7					50	55 6	
	8						50		
	10						50 5		
Dog 2		7	2				48	50	
		4½					63	58 8	
		6					47 7	55 5	
	10						47 7		
	11						55 5		
	7						50		
Dog 3		3½	2			50 9	37 6	52 6	64
	12	5					41 7	61 7	
	7	5½					43 5		
	7	(*)					37 9		
Dog 4		6					45 9		
(Pregnant)	7	4½					53 8	64	
	8	6					50		
	8	4		10 9	26 3				
	5½	4½		10	22 4				
	6	3½		10	45 4				
Dog 5		5	2			58 3	50	64 9	71 3
	8½	5					37	58 8	
	7	5		20			62 8	68	
	8	4		17 7	51			66 6	
		5½			45 8				

(*) Not read

EXCRETION IN NORMAL INDIVIDUALS AND VARIATIONS DEPENDENT ON METHODS OF ADMINISTRATION

The excretion has been studied in several hundred normal individuals In our earlier work subcutaneous administration was used exclusively

the drug appearing in the urine in from five to eleven minutes, 40 to 60 per cent (average 50 per cent) being excreted in the first hour after its appearance in the urine, and 60 to 85 per cent for two hours In health the elimination is practically completed in two hours, only a trace being present during the third and fourth hours

On account of the large variations in excretion in normal individuals following subcutaneous administration, it was thought a large part of this variation might be due to tardiness of absorption The excretion following intramuscular (gluteal and lumbar) injection was consequently investigated After gluteal injection (thirteen readings in twelve individuals) variations from 41 7 to 62 5 per cent were encountered (Table 4) for one-hour readings (ten minutes being allowed for time of appearance) an average of 51 per cent being eliminated

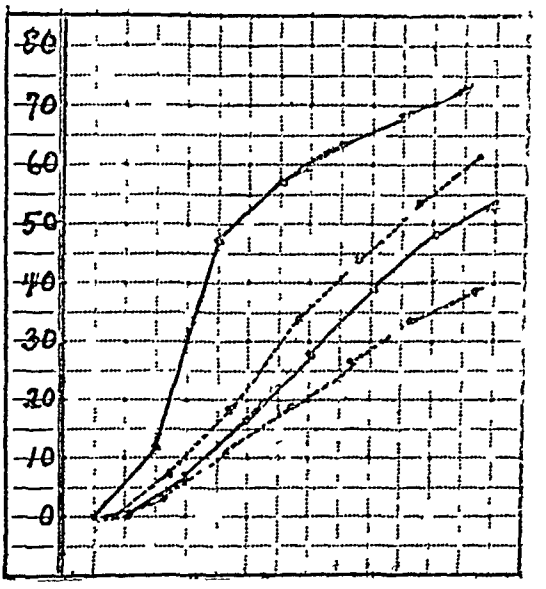

Chart 2.—Curve of excretion in a man for one hour, estimations being made at ten-minute intervals Upper black line represents excretion following intravenous injection, upper dotted line, excretion following lumbar injection, lower black line excretion following gluteal injection, and the lower dotted line represents excretion following subcutaneous injection

In twenty-one readings on fourteen normal individuals the variation following lumbar injection (Table 2) was from 51 8 per cent to 64 1 per cent, except in Case 10, in which the first test read 40 2 per cent, and there being some doubt as to the accuracy of the technic, three subsequent control injections were given showing an output of from 60 to 61 per cent on each occasion The average output of the twenty readings was 57 5 per cent This would seem to indicate *that absorption plays but a small rôle in affecting the accuracy of the test when one-hour determinations following intralumbar injections are employed*

TABLE 2.—INTRAMUSCULAR INJECTION, LUMBAR

Case		Time of Appearance, Minutes	Percentage Excreted—1st Half Hour	Percentage Excreted—2nd Half Hour	Percentage Excreted—1 Hour
1	G	8	35 7	16 1	51 8
2	D	6	19 2	35 7	54 9
3	O	6	45 8	16 6	62 4
4	S	7	32 5	21 8	54 3
5	G	7	32 3	26 3	58 6
6	M		32 3	21 7	54
			33 3	21	54 3
7	Y	7	26 3	26 3	52 6
8	N	6	33 3	29 8	63 1
9	J	8	29	25	54
10	M	7	23	17 2	40 2
		8			60 9
					60 2
					60 2
11	S	6			61 7
					64 1
		7	38 8	24 4	63 2
12	G	8			51 8
13	R	5			62 5
					62 5
14	G	8	34	26 2	60 2
	Average				57 4

TABLE 3.—INTRAVENOUS INJECTION IN NORMAL CASES

Case		Time of Appearance, Minutes	Percentage Excreted—1st Half Hour	Percentage Excreted—2nd Half Hour	Percentage Excreted—1 Hour
1	U	5	56 8	23 3	80 1
2	L C	4	53 2	10 8	64
3	S B	4	66 6	13 4	80
4	K	?			70
5	S	3½			62 5
		4			62 5
		4			63 3
6	D	4			70
7	L		58 8	13 2	72
8	C		64 1	13 8	77 9
9	S	*	46 7	11 1	57 8
10	J		55 5	9	64 5
			62 5	10 2	72 7
11	P	6½			66 6
12	M	4			62 5
					65 8
					65 5
13	S	4			62 5
14	Y	4			71 5
					68 5
	Average				67 9

*Question as to being normal

Intravenous injections have been employed (Table 3) with three ideas in view, namely in order to determine, first the total excretion for one hour, second what variations in kidney function existed in normal individuals, and third to what extent absorption was responsible for variations in excretion The output for one hour (twenty readings in

fourteen individuals) averaged 67 9 per cent, considerably higher than that from other methods of administration The excretion varied from 62 5 to 80 per cent, with one exception, No 9, who excreted 57 8 per cent This individual gave a somewhat low output following all methods of administration, although no other evidence of renal disease could be discovered

Table 4 shows the variations in percentage excretion for one-hour periods in the same individuals following subcutaneous, gluteal, lumbar and intravenous administration

TABLE 4.—EXCRETION IN NORMAL INDIVIDUALS FOLLOWING FOUR DIFFERENT METHODS OF ADMINISTRATION

Case		Subcut 1 hr %	Intramuscular gluteal 1 hr %	Intramuscular lumbar 1st half hr %	Intramuscular lumbar 2nd half hr %	Intramuscular lumbar Total for 1 hr %	Intravenous 1st half hr %	Intravenous 2nd half hr %	Intravenous Total for 1 hr %
1	C	53 2	62 5				64 1	13 8	77 9
2	L		58 9				58 8	13 2	72
3	S	35 7	47 6				46 7	11 1	57 8
4	S	52 6	53 7						62 5
									62 5
									63
5	S B	38 8					66 6	13 4	80
6	U	41 6	49				56 8	23 3	80 1
7	M								62 5
		43 1	43 4	32 3	21 7	54			65 8
		58 8		33 3	21	54 3			65 5
8	S	42 7	47 6						62 5
9	Y	60 9	41 7	26 3	26 3	52 6			71 5
		44 3							68 5
		45 5							
10	B	42	57 7						

By studying the curve of excretion (Chart 1) for five- and ten-minute intervals it was found, however, that from 30 to 35 per cent is excreted in the first ten minutes after appearance, this being half the total excretion for one hour It at once becomes apparent, this being true, that observation for one-hour periods are subject to the same criticism that would apply to observation over four or five hours following subcutaneous injection or a study of total excretion When intravenous administration is employed, observation for more than one-half hour should not be used, the amount of excretion for this time being almost equal to that for two hours following the subcutaneous injection It has yet to be determined if the same reliance can be placed on the intravenous readings as can be placed on the subcutaneous, or especially on the lumbar method of administration, as well as what decrease in excretion occurs in disease following the intravenous administration †

†Further investigation has shown that the intravenous method of administration is not as accurate as the intramuscular, especially where ureter collecters are employed The normal variations in the functioning power for such short periods as fifteen minutes or one-half hour are too great

The striking rapidity of elimination in the first few minutes following intravenous injection results, of course, from the concentration of the drug in the circulation, each cubic centimeter of blood going to the kidney-cells carrying more phthalein than by any other method of administration

THE INFLUENCE OF VARIOUS DIURETICS ON THE EXCRETION OF SULPHONEPHTHALEIN

Because of the fact that many of the patients on whom the functional test is made are renal, cardiac, or cardiorenal cases, and therefore the subjects of an induced diuresis, it becomes at once desirable to know what influence these various diuretics exert on the secretion of the drug in the urine, or, in other words, what changes in renal function, as indicated by the test, occur under the influence of diuretics and to what extent these changes occur

A study of the influence of diuretics is of value from another point of view, inasmuch as the processes whereby diuresis is induced vary considerably with the different classes of diuretics, consequently allowing inferences to be drawn regarding the mechanism of excretion of sulphonephthalein from the influence these various classes exert on its excretion

Two methods of ascertaining the influence exerted by diuretics have been used

1 The effect of their administration on the output of sulphonephthalein in cats which received a constant inflow of sulphonephthalein

The method here adopted was as follows Cats were lightly etherized and given by stomach-tube 0 25 gm chlorbutanol (known commercially as chloretone) per kilo (The chlorbutanol was finely ground in a mortar and then washed into the stomach with 50 to 100 c c of water) The cats were allowed to come out of the influence of the ether and were not used until one and one-half or two hours had elapsed Into one femoral vein was inserted a cannula which was attached to a burette filled with a solution of phenolsulphonephthalein Into the other femoral a cannula attached to a three-way stop-cock was inserted After tying the neck of the bladder a small glass cannula with a capacity of only two or three drops was tied into an opening in the bladder in such a way that the open flanged edge of the cannula came in apposition with the two ureteral openings, the apposition being such that in many instances on compression of the bladder-wall over the bell of the cannula, not a drop, or at most only one or two drops of urine could be pressed from the distal end of the cannula The abdominal wall was closed except at the exit of the bladder cannula and an incandescent electric light was placed just a few inches above the animal the whole being covered with a large towel in order that the body temperature be maintained

Under such conditions it was found that an excellent urinary secretion could be constantly obtained for long periods Many of the animals having been given another small dose of chloretone together with hot milk by stomach-tube at the end of a day's experiment were found in such good condition the following morning that observations were continued throughout the second day

From the burette the solution of sulphonephthalein was allowed to run into the femoral vein, 6 mg of the drug being administered at the first injection The phthalein was dissolved in either 0 8 per cent salt or in Ringer's solution, in some instances 0 6 mg to c c, in others 2 mg to the c c The time elapsing before the appearance of the drug in the urine was noted, this being usually from one and one-half to four minutes Collections were then made usually for fifteen-minute periods, occasionally for twenty, and in one or two instances for one-half hour periods At the end of each period the receptacle into which the urine drained was changed and sulphonephthalein was again allowed to run into the vein, a constant amount, usually 1 8 mg, for each period Where the period of collection was longer the amount of phthalein injected was of course greater, as for instance in Experiment 23, the amount of phthalein injected each period being 3 mg in 1 5 c c Ringer's solution and the period of each collection one-half hour

Collections were made for three or four such periods prior to administering any diuretic in order that an idea of the average excretion for each period could be had for comparison with the output under the influence of the diuretic It was found that in some instances the output of phthalein remained approximately the same over periods of one to one and one-half hours, although the output of urine varied considerably

The diuretic was now administered through the other femoral vein and its influence on the amount of urine, the amount of sulphonephthalein as estimated by the Duboscq colorimeter and on the reaction of the urine noted (sulphonephthalein serving as the indicator), observation in many instances covering a period of four to eight hours

The accompanying charts represent the results obtained in some of these experiments *Each period lasted fifteen minutes, unless otherwise stated*

Caffein—This exerts a stimulating influence on the secretory cells of the renal tubules and increases their secreting power, von Schroeder,[11] Anten,[12] Ach[13] and Sullis[14] have demonstrated this unquestionably for the frog's kidney and the same presumably holds for mammals Undoubtedly it is true that other factors, such as change of blood-pressure and increase in rate of flow through the kidney

11 v Schroeder Arch f exper Path u Pharm, 1886, xxii, 39, and 1887, xxiv, 85

12 Anten Arch internat de pharmacodyn, 1901, viii, 453

13 Ach Arch f exper Path u Pharm, 1900, xliv, 319

14 Cullis Jour Physiol, 1906, xxxiv, 250

(Ach,[13] Fletcher, Henderson and Loewi[15]) are additional and important factors in the production of diuresis The excretion of the solids under the influence of caffein (von Schroeder,[11] Loewi[16]) as well as the water output is augmented Barcroft and Straub[17] show that there is a temporary increase in the metabolism followed by a decrease under the influence of this drug

The effect of caffein on the excretion of sulphonephthalein is indicated in Experiment 14, Chart 3 The average output prior to the administration of caffein was 1 2 mg for each fifteen minutes, and after the administration 1 5 mg for the same length of time Marked diuresis under the influence of caffein is therefore associated with an appreciable increase in the phthalein output

Sodium Chlorid—A rational explanation of saline diuresis is that advanced by Cushny[18] The presence of hypertonic sodium chlorid in the blood disturbs the osmotic relationship and results in a great influx of water into the blood from

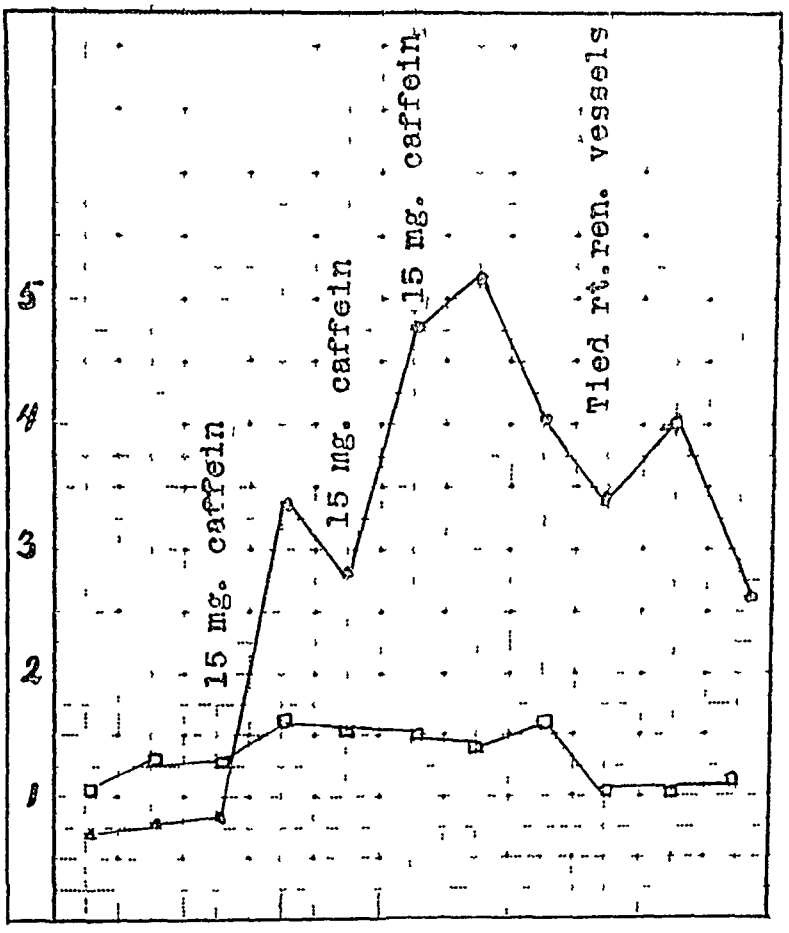

Chart 3—Experiment 14 Cat Chlorbutanol anesthesia Influence of caffein on urine output, phthalein excretion and reaction of the urine In this and the following charts the line with solid dots indicates c c of urine per period and the line with rectangles indicates mg of phthalein excreted per period

the lymph spaces hydremia resulting The hydremia causes an increase in the capillary pressure in the glomeruli which in turn promotes the escape of fluid into the capsule The resulting diluted urine rapidly flows through the tubules a short time only being presented for reabsorption, a marked increase in the

15 Loewi Arch f exper Path u Pharm 1905 liii, 15
16 Loewi Arch f exper Path u Pharm 1902 xlviii 411
17 Barcroft and Straub Jour Physiol 1911 xli 145
18 Cushny Jour Physiol 1901 xxvii 449, and 1902 xxviii 431

amount of urine secreted therefore results This is a purely mechanical process and can be reproduced point for point in the dead animal (Sollmann)

Hypertonic sodium chlorid, even when the diuresis is enormous, causes no increase in output of sulphonephthalein, indeed the average output for fifteen-minute periods is slightly decreased from 1 25 mg before to 1 15 mg after the administration (Chart 4, Experiment 12) We know that the output of sodium chlorid under the conditions of this experiment is greatly increased and therefore conclude that the excretion of phthalein bears no relation to sodium chlorid excretion

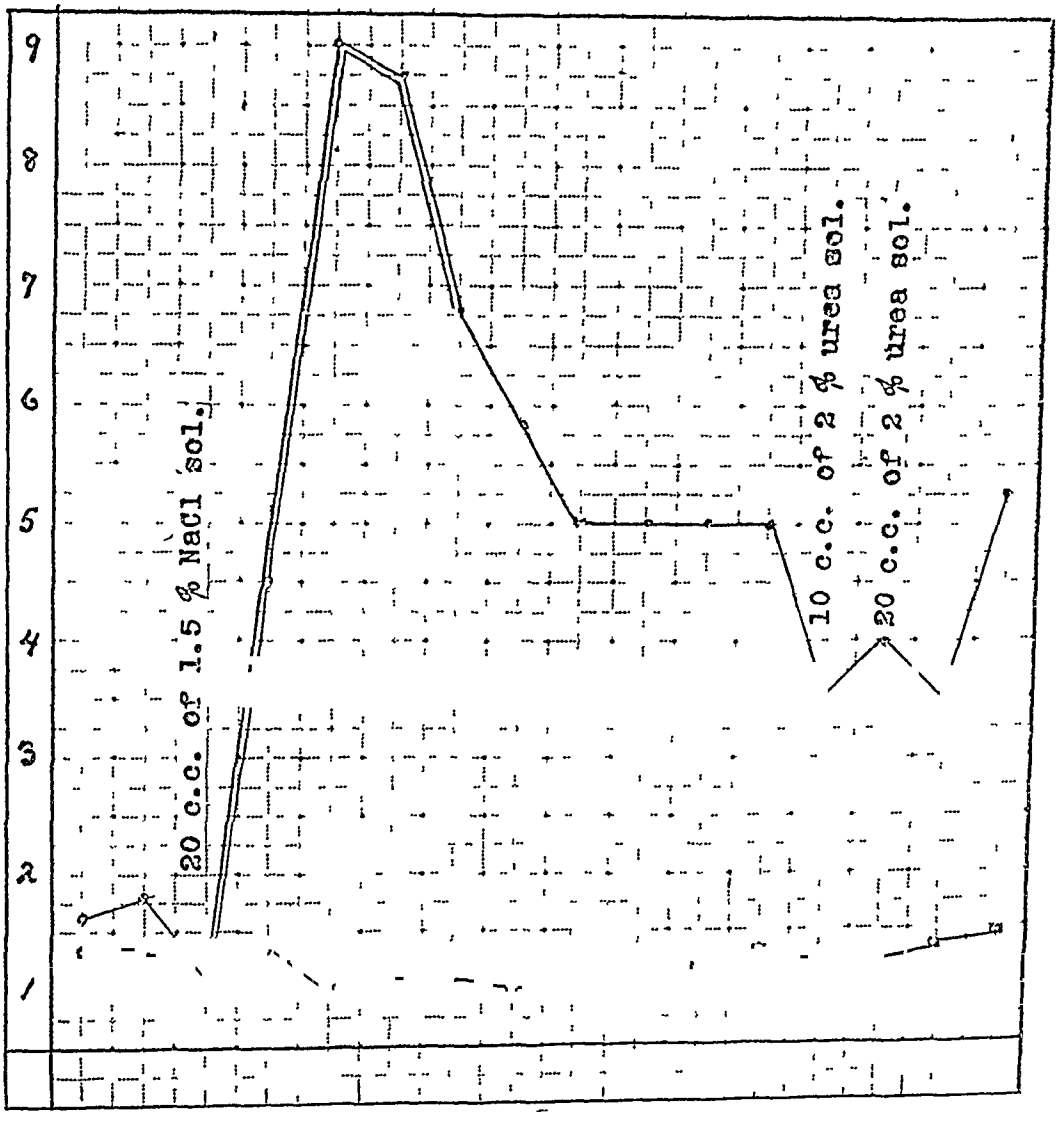

Chart 4 —Experiment 12 Cat Chlorbutanol anesthesia Effect of sodium chlorid and urea on urine output, phthalein excretion *and reaction of the urine* In addition to the lines already explained the double line in this and following charts indicates distinct alkalinity of the urine

Urea —Urea being a diffusible substance has been thought to produce diuresis in the same manner as sodium chlorid, that is by salt action The work of Cullis, however, which we are able to confirm, shows that in the frog's kidney, when only the tubules are allowed to participate in the formation of urine, salines fail to produce diuresis, whereas urea elicits an abundant secretion This certainly indicates that the action of urea differs somewhat from that of sodium

chlorid, in fact, it indicates that urea exerts a stimulating effect on the cells of the renal tubules just as caffein does Furthermore, Barcroft and Straub have shown that during urea diuresis, more than the normal amount of work is per-

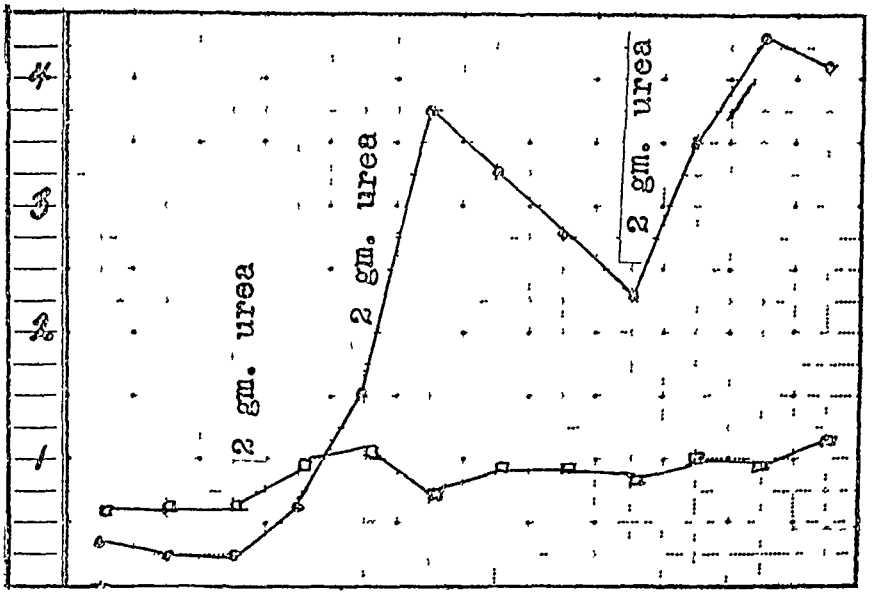

Chart 5—Experiment 18 Cat Chlorbutanol anesthesia Effect of urea on urine output, phthalein excretion and reaction of the urine

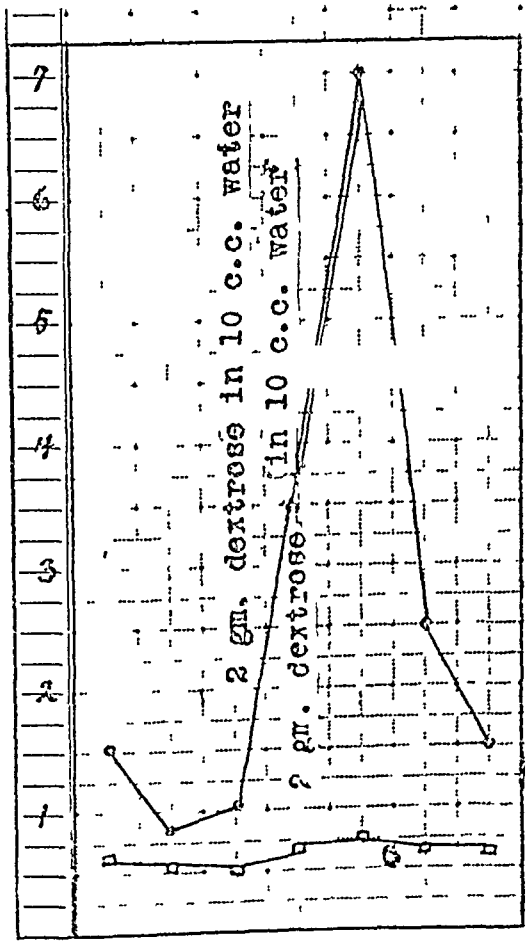

Chart 6—Experiment 22 Cat Chlorbutanol Effect of dextrose on urine output, phthalein excretion and reaction of urine

formed by the cells of the tubules, no such increase being demonstrable during the course of a saline diuresis The fact that urea increases the excretion of sulphonephthalein while sodium chlorid does not influence it at all, or decreases it, also suggests that a difference in the method of action exists Whereas in our experiments sodium chlorid diuresis was accompanied by the early appearance of alkalinity which persisted for a long period, alkalinity was obtained only

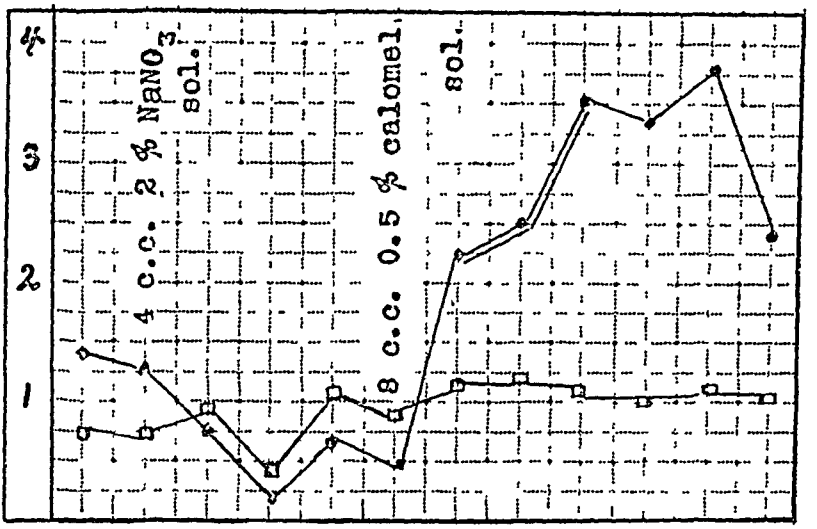

Chart 7 —Experiment 6 Cat Chlorbutanol anesthesia Effect of calomel on urine output, phthalein excretion and reaction of urine Each period twenty minutes

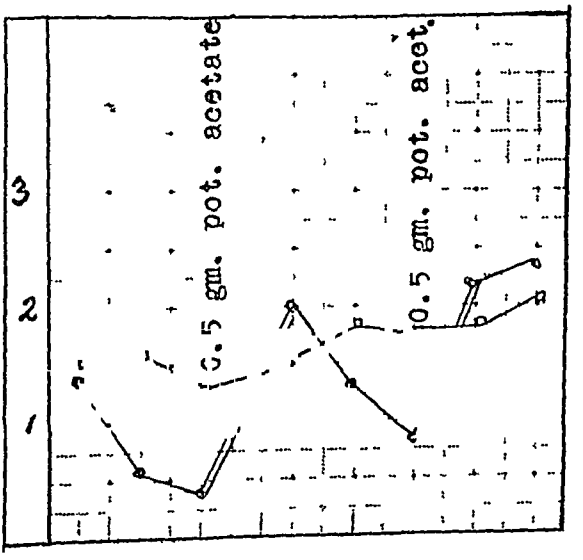

Chart 8 —Experiment 20 Cat Chlorbutanol anesthesia Effect of potassium acetate on urine output, phthalein excretion and reaction of urine

with considerable difficulty during the urea diuresis, which is another point indicating difference in method of action In one experiment (Chart 4) a slight decrease in the phthalein excretion under the influence of sodium chlorid and at the same time a slight increase under the influence of urea, while Chart 5, another experiment, shows a very definite increase in phthalein output under a urea diuresis The difference in the alkalinity in the two experiments is striking

Dextrose—Dextrose resembles urea closely in its action It is also capable of stimulating secretion by the tubules in frogs as was shown by Cullis[14] Chart 6, Experiment 22, indicates that it also slightly increases the phthalein excretion

Calomel—Calomel is classified as an irritant diuretic raising the glomerular pressure by dilating the renal arterioles It possibly stimulates also the vital secretory function of the renal cells This latter is suggested by the decided increase of phthalein excretion in Chart 7, Experiment 6

Potassium Acetate—Although this is supposed to exert only a salt action, it will be seen from Chart 8, Experiment 20, that an increased phthalein output was elicited

Digitalis—Digitalis produces diuresis entirely through circulatory changes, i e, increase in heart action and increased blood-supply regardless of the slight vasoconstriction which accompanies its use The solids may not share at all in the diuresis They remain the same or at most are but slightly increased The phthalein output does not increase under the influence of digitalis, in some cases

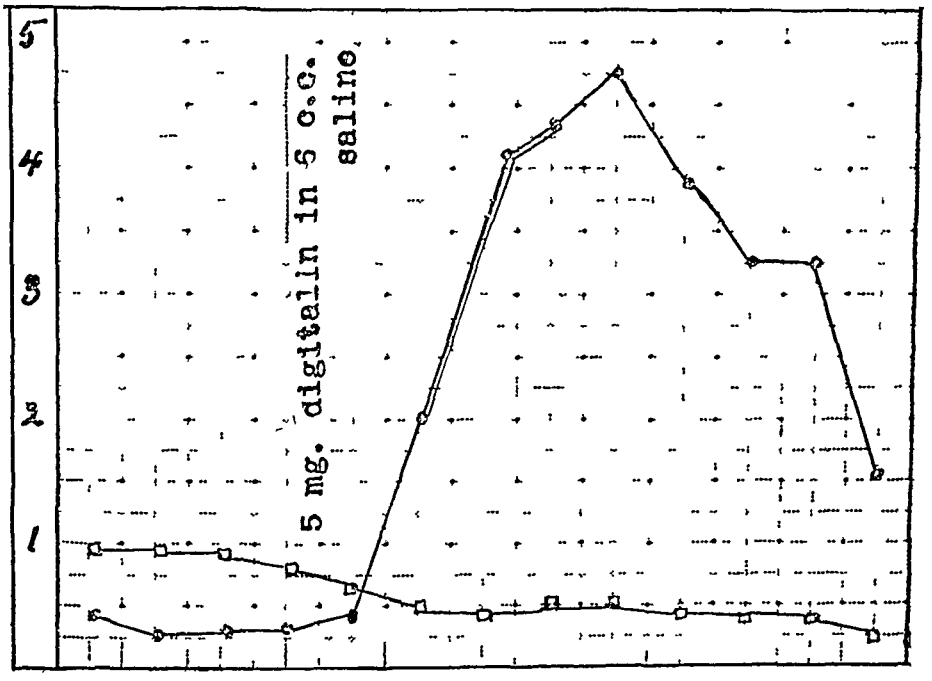

Chart 9—Experiment 8 Cat Chloributanol anesthesia Effect of digitalis on urine output, phthalein excretion and reaction of the urine

remaining the same In one instance a decided decrease was encountered during the course of a marked diuresis (Chart 9, Experiment 6)

Phlorhizin—According to Loewi[19] this is not a direct diuretic, the diuresis really resulting from a loss of reabsorption power in the tubules Cullis,[14] on the other hand, shows that it has some direct stimulating effect on the tubules and also that by perfusing it through the frog's kidney a reducing body can be obtained The work of Barcroft and Straub[17] also indicates that the secretion is an active process As will be seen in Chart 10 Experiment 23, a slight increase from 1 75 to 1 93 mg for one half hour periods was obtained following its use

Ringer's Solution—Only a slight diuresis was obtained with Ringer's solution (see Chart 11, Experiment 21), and at the same time practically no effect on the phthalein output Urea in this instance did not increase the phthalein output, this being the one instance in five experiments

Potassium Nitrate—Under the conditions of the experiment this salt produced diuresis while sodium nitrate failed on several occasions The potassium ion must therefore play some rôle in the production of diuresis as well as the nitrate ion The salt as a diuretic falls into the same group as the sodium chlorid

19 Loewi Arch f exper Path u Pharm 1903 l 326

Practically no influence is exerted on the phthalein excretion (Chart 12, Experiment 30), the average output before and after being 1 08 mg

Under the conditions of our experiments it was found that those diuretics which are known to exert some stimulating influence on the activity of the secreting cells, or those diuretics in connection with which evidence is at hand indicating a stimulating action on the secreting cells

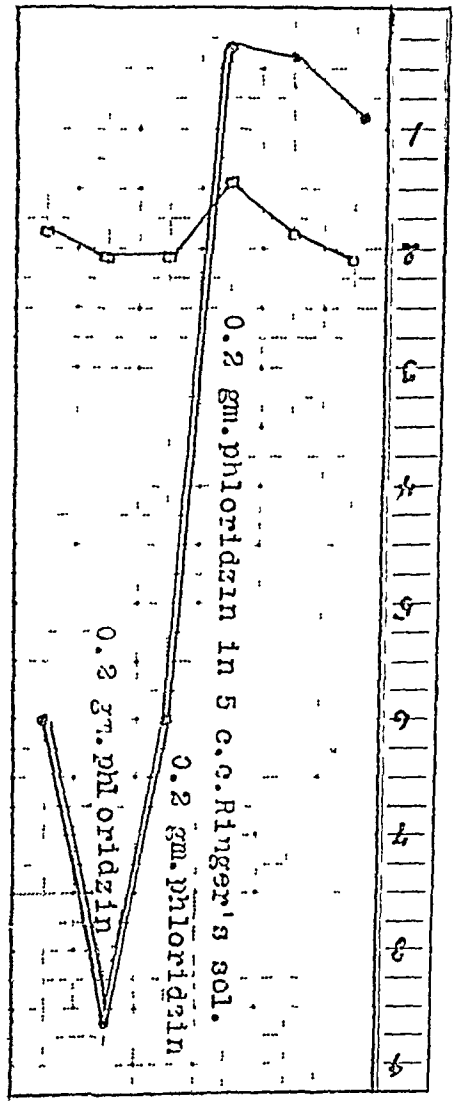

Chart 10.—Experiment 23 Cat Effect of phlorhizin on urine output, phthalein excretion and reaction of the urine Each period one-half hour

(caffein, urea, dextrose, phlorhizin, calomel), slightly increase the phthalein output, whereas those diuretics which act entirely by changes in osmotic tension or by changes in blood-pressure, etc (hypertonic sodium chlorid solution, potassium nitrate and digitalis), apparently have little or no effect on its excretion

THE EFFECTS OF DIURETICS ON PHTHALEIN EXCRETION IN NORMAL INDIVIDUALS

The phthalein excretion following intramuscular (lumbar) injection was studied in a number of normal individuals who were then given by mouth various diuretics in the usual dosage for twenty-four hours previous to repeating the test The collections were made for one hour following the time of appearance of the phthalein in the urine The drugs employed were digitalis, calomel, diuretin, caffein, the ward

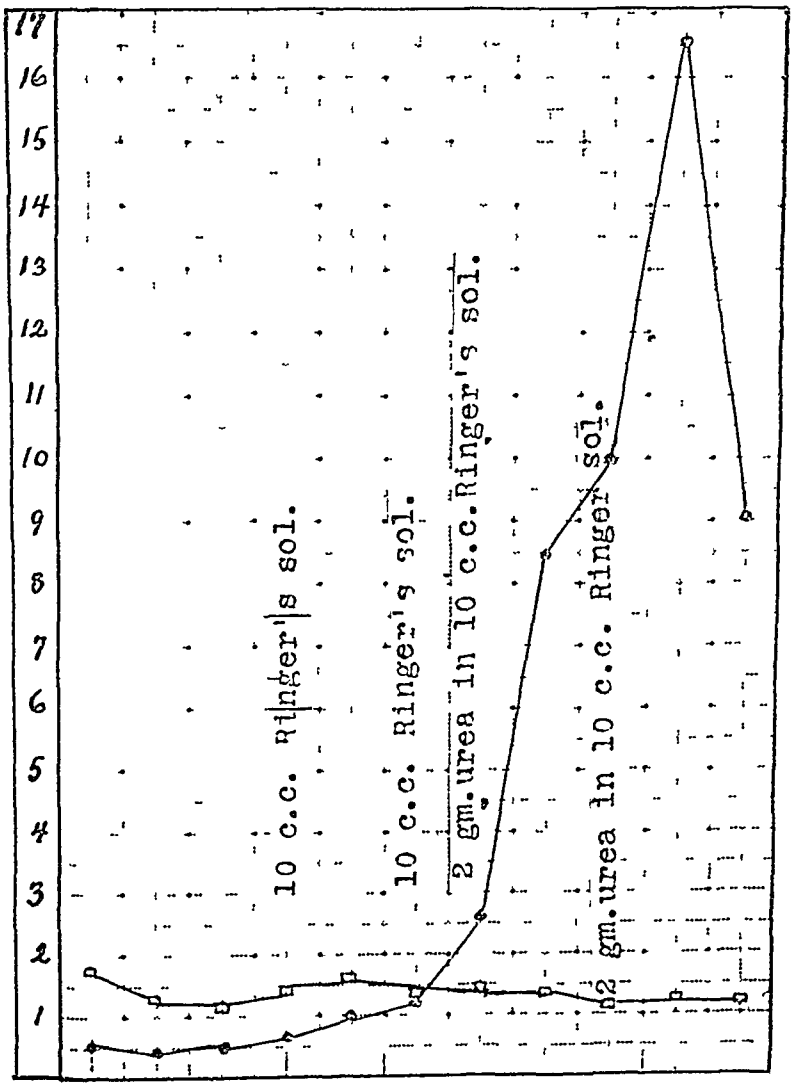

Chart 11 —Experiment 21 Cat Chlorbutanol anesthesia Effect of Ringer's solution and of urea on the urine output and phthalein excretion

diuretic[20] usually employed at the Johns Hopkins Hospital, and Basham's mixture of iron

20 Ward diuretic

Potassii Acetatis	ʒiv
Tr Scillæ	ʒiij
Spts Etheris Nitrosi	ʒiv
Aquæ q s ad	ʒiv

Misc —Sig ʒii t i d

The results obtained may be seen in Table 5 No appreciable effect on phthalein excretion could be detected in any instance with the ordinary therapeutic dose Relatively much larger doses were used in the animal experiments

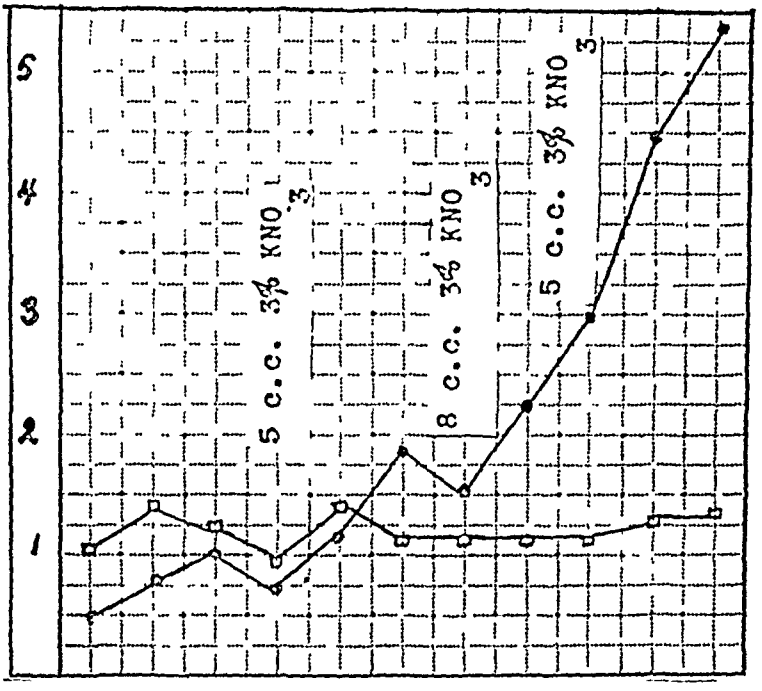

Chart 12.—Experiment 30 Cat Chlorbutanol anesthesia Effect of potassium nitrate on the urine output and phthalein excretion

TABLE 5.—EFFECTS OF VARIOUS DIURETICS ON PHTHALEIN EXCRETION IN NORMAL INDIVIDUALS, FOLLOWING INTRAMUSCULAR (LUMBAR) INJECTIONS OF PHTHALEIN

Name	Normal Excretion Per cent	Diuretic	Excretion After Diuretic Per cent
R	62 5	Caffein gr iii, t i d	62 5
M	60 2	Diuretin gr xv, q 4 hr for 24 hrs	60 9
M	60 2	Calomel gr 1/10, q ½ hr up to 8 doses Test 2 hrs after last dose	60 2
S	63 2	Diuretin gr xv, q 4 hr for 24 hrs	61 7
S	63 2	Caffein gr iii, t i d for 24 hrs	64 1
W	48	Basham's mixture 5ii, q 4 hr for 24 hrs	51 5
F	56 4	Ditto	56 2
S	46 7	Ward diuretic 3ii, q 4 hr	46 5
Y *	60 9	Tr digitalis m xv, q 3 hr for 8 doses	60 2
	45 5		
	66 6		

*Subcutaneous injections

THE INFLUENCE OF DIURESIS ON THE REACTION OF THE URINE

In 1872, Falck[21] called attention to the fact that the urine becomes alkaline following the administration of large amounts of salt solution

21 Falck Virchow's Arch f path Anat, 1872, lvi, 315

by stomach or intravenously Gruber[22] recorded similar observation in 1887 In his work on caffein, von Schroeder[11] encountered the same phenomenon invoked by this diuretic when the nerves to one kidney were destroyed The urine from the side with diuresis was alkaline, that from the other side was still acid

Rudel,[23] in 1892, made a careful study of this subject working with numerous diuretics and found that alkalinity very commonly resulted Katsuyama[24] studied particularly the influence of caffein, urea and diuretin in this respect Under their influence the alkali, estimated as "alkaline chlorids," is greatly increased, sodium oxid is always increased, potassium oxid may or may not be increased, and these changes can occur under the influence of caffein even without marked diuresis Urea increases the chlorin and sodium oxid and alkaline chlorids only slightly Diuretin increases markedly the alkalinity, as "alkaline chlorids," chlorin, potassium oxid, sodium oxids are all increased

A change in reaction (alkaline urine) has been noted in many of our diuretic experiments We have noted it after destroying the nerve connections of one kidney in two instances even when diuretics were not administered In two other instances under similar conditions it failed to appear

Under the conditions of our experiments, as set forth in the description of our work with diuretics on cats, alkalinity of the urine is indicated by the urine assuming a purplish-red color The ease with which a change in reaction is invoked varies very considerably with the various diuretics

THE SPECIFICITY DISPLAYED BY THE KIDNEY IN THE EXCRETION OF PHTHALEIN AND THE CONCENTRATION CAPACITY OF THE KIDNEY IN THIS REGARD

Six mg of phthalein given subcutaneously to a patient weighing 60 kilo yields a dilution in the body of 1 in 10,000,000 An infinitely dilute solution is presented to the kidney, which within one hour under normal conditions picks out 50 per cent of these circulating molecules and passes them on into the urine, sometimes as much as 3 mg being excreted in 12 c c of urine—a dilution of 1 in 4,000, or 2,500 times the concentration in the blood When the amount of blood only is considered in the question of dilution, the concentrating power still remains several hundred, for when 6 mg is given intravenously as much as 20 per cent can be recovered in five minutes in 2 or 3 c c of urine

At the same time in either instance, the same concentration is presented to the liver to the pancreas salivary glands, etc and yet only

22 Gruber Ludwig Festschrift 1887 quoted from Rüdel
23 Rüdel Arch f exper Path u Pharm, 1892 xxx 41
24 Katsuyama Ztschr f physiol Chem 1899 xxviii 587 1901 xxxii, 239

a small amount appears in the bile, while not a trace of it can be found in the pancreatic juice or saliva The capacity of picking out the molecules of sulphonephthalein from infinitely dilute solution and passing them on into the secretion in comparatively concentrated solutions is therefore a function specific to the kidney

MECHANISM OF EXCRETION OF SULPHONEPHTHALEIN

The ideal method of determining the mechanism whereby a dye substance is excreted is that which was adopted by Heidenhain,[25] in his work with indigo-carmin, i e, to remove the kidney during the active secretion of the dye, fix the dye *in situ,* make sections and demonstrate the presence of granules of the dye in the cells actually engaged in excreting it By this method he demonstrated that indigo-carmin was excreted by cells of the tubules

This method cannot be utilized in connection with phenolsulphonephthalein, as all of the ordinary fixatives fail to fix this dye in the cells Consequently it was found necessary to attempt to ascertain by other methods which part of the excreting mechanism is concerned in the excretion of this body

EXCRETION BY THE FROG'S KIDNEY

The work of Nussbaum[26] indicating that the renal tubules in the frog's kidneys are supplied by the renal portal system, which is entirely separate and independent of the arterial supply to the glomeruli, although discredited by Adami,[27] was later shown by Nussbaum[28] and by Beddard[29] to be absolutely correct The work of Cullis also affords striking confirmation

Advantage was taken of this independence of circulation to the tubules in the frog's kidney, in an attempt to discover the method of excretion of sulphonephthalein

Large male frogs, *Rana catesbiana,* weighing about 300 gm, were pithed, the abdomen opened by long incisions on each side of and parallel to the anterior abdominal vein The left kidney was exposed and all the arterial connections severed by means of the Paquelin cautery, as suggested by Beddard A cannula was then inserted into the anterior abdominal vein and a small glass catheter inserted into the left ureter A protocol will indicate the course of the experiment and the results obtained

Ringer's solution was perfused from a Mariotte flask through the renal portal system under a pressure of 35 cm of water Perfusion from

25 Heidenhain Herman's Handbuch der Physiologie, v, 348
26 Nussbaum Pfluger's Arch, 1878, xvi, 139, and 1878, xvii, 580
27 Adami Jour Physiol, 1886, vi, 382
28 Nussbaum Anat Anzeiger, 1886, i, 67
31 Beddard Jour Physiol, 1902, xxviii, 20

the renal portal vein for about fifteen seconds every three minutes was begun at 12 30 p m and continued until 2 25 p m, no flow of urine resulting At 2 25 the same solution, but now containing 1 5 per cent urea and also phenolsulphonephthalein (60 mg to 100 c c), was perfused Diuresis became apparent at 2 40 p m At 3 50 p m the urine reached the distal end of the catheter and was found to contain considerable phthalein At 4 10 p m a saturated aqueous solution of Prussian blue was injected, the kidney immediately removed and placed in absolute alcohol Serial sections were later made but not a trace of blue could be found in any of the glomeruli Identical results were obtained on adding caffein to Ringer's solution during the course of a purely venous perfusion

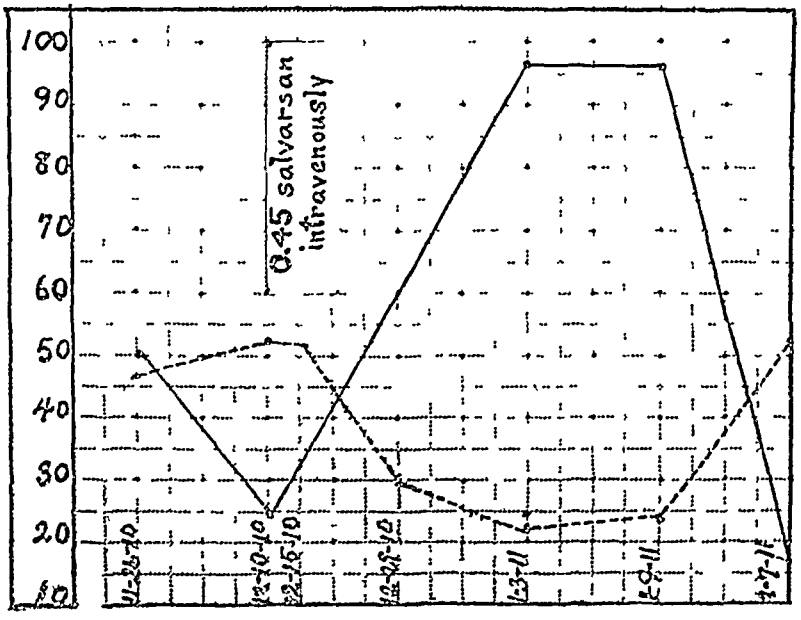

Chart 13 —The dotted line represents the phthalein excretion and the black line the amount of albumin in the urine in grams per liter

This furnishes absolute proof that *phenolsulphonephthalein can be excreted by way of the cells of the tubules* in the frog and presumably the same holds true for mammals

In another frog a purely arterial perfusion, by the method of Cullis, was made with hypertonic sodium chlorid solution Here also the phthalein was excreted, but under these conditions both tubules and glomeruli participate

THE INFLUENCE OF ANEMIA

Barcroft and Straub[17] have shown that after excluding the function of the renal tubules by profuse bleeding and the administration of large quantities of Ringer's solution, an isotonic urine, a pure glomerular filtrate can be obtained The excretion of phthalein under such conditions was investigated A protocol of an experiment in this connection follows (Table 6).

Cat Weight, 2 8 kg Injection, 0 7 gm chloretone at 10 a m 12 26 injection of 6 mg sulphonephthalein intravenously At the end of each period 1 8 mg of phthalein was given

TABLE 6.—EXCRETION OF PHTHALLIN AFTER EXCLUSION OF FUNCTION OF RENAL TUBULES BY BLEEDING

	Time	Quantity of Urine in c c	Mg Phthalein Excreted
	12 43 p m	0 6	1 026
	12 58	0 6	0 951
	1 13	0 7	1 020
	1 28	0 6	0 789
	1 44	0 6	0 918
	1 58	0 8	0 714
1	1 53—bled 33 5 c c and injected 40 c c Ringer's solution + 0 6 mg phthalein extra		
	2 13 p m	0 2	0 357
	2 28	1 2	1 128
	2 43	1 8	1 128
2	2 42 2 47—bled 40 c c and injected 50 c c Ringer's		
	2 58	0 9	0 618
	3 13	1 4	0 999
3	3 08 to 3 12—bled 30 c c and injected 50 c c Ringer's + 0 6 mg phthalein extra		
	3 28	0 6	0 375
	3 43	0 4	0 300
	3 43 given 15 c c Ringer's solution		
	3 58	0 4	0 234
	4 08 given 20 c c Ringer's solution		
	4 14	0 4	
	4 29	0 8	0 267
4	4 37—bled 35 c c and given 20 c c Ringer's solution		
	4 47	0 9	0 270

The blood withdrawn was centrifuged and the amount of phthalein per cubic centimeter estimated, showing that the amount of drug in the blood increased considerably during the experiment, at first examination containing 0 0068 mg per cubic centimeter, and in the last 0 0136 mg per cubic centimeter

In this experiment after profuse hemorrhage the excretion of phthalein decreased to approximately one-fourth of what it was normally, while at the same time the concentration of the drug in the blood was doubled, so that with severe anemia the excreting power of the kidney was decreased to one-eighth of normal

Unless the bleeding be very profuse, however, little effect on the phthalein excretion will be noted, as can be seen from the preceding protocol (Table 8) and from the following protocol as well as from clinical evidence which will be presented later

Cat.—Weight, 2 8 kg Under chloretone anesthesia

12 10 p m.—5 c c 4 per cent sodium chlorid solution

12 26 p m.—6 mg phenolsulphonephthalein intravenously Drug appeared in urine in two minutes and 18 per cent was excreted in sixty six minutes

4 50 p m.—50 c c of blood withdrawn and 60 c c of Locke's solution introduced in its place

10 15 p m—10 c c of 4 per cent sodium chlorid
10 24 p m—6 mg of sulphonephthalein administered Drug appeared in two minutes and 27 per cent was excreted in sixty-six minutes

These results show that moderate degrees of anemia do not interfere with the excretion of phthalein, but that very severe degrees of anemia, which Straub and Baicroft have shown to result in the entire removal of the tubular function of the kidney, materially decrease the output of phthalein This would indicate that the tubules are concerned in the excretion of phthalein but at the same time shows that the glomeruli also are capable of excreting some of this drug

OTHER PHENOMENA BEARING ON THE METHOD OF EXCRETION OF SULPHONEPHTHALEIN

The fact that the output of phthalein bears no relation to the excretion of water and chlorids also suggests that the glomeruli play only a minor rôle in its excretion

It is asserted by McKnider[32] that in experimentally induced acute tubular nephritis (produced by mercury bichlorid and by potassium chromate — see Schlayer and Hedinger[33]), there is a marked diminution in the excretion of phthalein, while in the vascular type (produced by cantharides or arsenic) little or no decrease occurs at first but a decrease does occur later[34] This also suggests that the glomeruli play a subsidiary rôle in the phthalein excretion

The findings in our work with diuretics (discussed above) i e, that those substances which probably act by stimulating into activity the renal cells, increase the phthalein output, while those diuretics which act only mechanically, as by changes in blood-pressure or in osmotic tension, do not influence the phthalein output, gives additional confirmation to the theory of activity on the part of the cells of the tubules in the excretion of phthalein

THE STUDY OF NEPHRITIS

Heretofore functional tests have not been considered of any great value to the clinician in relation to nephritis In fact hyperpermeability[35] to methylene-blue, indigocarmin and rosanilin has been shown to exist in acute and in chronic parenchymatous nephritis, while, on the other hand, decreased permeability with slow appearance and prolonged excretion has been demonstrated in the chronic interstitial variety

32 McKnider Personal communication
33 Schlayer and Hedinger Deutsch Arch f klin Med, 1907, xc 1 and xci
34 The excretion of this drug in experimental nephritides is now under study
35 For literature concerning other functional tests see our original article Jour Pharm and Exper Therap 1910 i, 579

ACUTE NEPHRITIS

Thus far we have had opportunity to study only five cases of acute nephritis

CASE 1.—The patient suffered from scarlatinal nephritis, had a severe angina and showed evidence of grave toxemia. It was impossible to determine whether the toxemia was due to the nephritis or to the angina. An injection of 6 mg. of the phthalein was followed by the appearance of the drug in the urine in twenty-three minutes. Forty-four per cent. of the drug was excreted in the

TABLE 7.—PARENCHYMATOUS NEPHRITIS

Name	Date	Clinical Condition	Time of Appearance (min.)	Am't of Urine (c.c.)	S. G.	Albumin
1—L., aged 35	12/6/09	Some edema and anemia	7			++
2—R., aged 35	12/10/09	Edema and mild anemia	30	10	1,032	++
	12/11/09		20	13		++
	12/13/09		16	50	1,012	++
	12/24/10	Better clinically	25	23	1,036	++
	12/29/10	Better clinically	20	50		++
3—R. L.	2/1/10	Symptoms two months, mild		114	1,017	++
4—W. L., aged 32	1/28/10	Fair condition	9	412	1,010	++
5—M., aged 31	3/5/10	Very mild symptoms, no edema, slight anemia	8	312	1,005	++
6—G., aged 34	3/15/10	Bad, mild uremia previous to admission	22	125	1,013	++
7—P., aged 35	2/1/10	Fair	6			
8—I. J., aged 30	4/4/10	Edema, anemia	10	305	1,007	+
9—P. S., aged 35 75362	11/7/10	Edema, anemia		263		+
10—M. A., aged 33 75555	11/6/10	Edema, dyspnea		134	1,011	++
	11/14/10	Apparently improved clinically		50		++
11—B.	11/14/10	Slight edema at times, no other symptoms		86	1,016	+
12—I. S., aged 57 75581	11/21/10	Edema, dyspnea		80	1,009	++
	11/30/10	Uremic		135	1,012	++
13—K.	11/23/10	Edema, slight		116	1,030	++
14—C., aged 30	11/26/10	Edema, anemia		168	1,030	++
	12/10/10			77	1,030	++
	12/29/10	Given 0.45 salvarsan 12/15/10				+++
	1/3/11	Clinical condition exceedingly grave		134	1,016	96 G. alb.
	1/9/11	No change		170	1,017	96 G. alb.
	1/17/11	Much better		226	1,018	+++
	2/7/11	Much better		166	1,024	++
15—S., aged 23	1/25/11	No symptoms, nephritis detected accidentally		112	1,022	+
	4/11/11	Intravenous injection	4	125	1,026	+
				230	1,010	+
16—S. P., aged 29 76996	2/10/11	Mild case		725		Alb. 6 G. to liter
	4/29/11	Labor induced five days previous to test on account of threatened eclampsia, fair condition				
17—Y., aged 48	3/10/11	High blood tension, anemia, some edema		374	1,008	+
18—Aged 28	7/7/10	Uremia, nausea and vomiting		100		++
19—D., aged 28	3/20/11	Edema, dyspnea, clinically grave		150	1,026	++
	3/28/11	About same condition		70	1,016	++
20—E. W., aged 25	4/21/11	No symptoms	7	73	1,014	+
	4/25/11	Lumbar injection				+
21—P. S., aged 40 77745	4/18/11	Edema, anuria for four days before admission		65	1,019	++
22—E. D., aged 19 77423	3/28/11	Backache, no other symptoms		200	1,015	+
23—Aged 23	5/8/11	Acute nephritis one year, no edema, blood-pressure 90 mm. Hg		400		5 G. to liter +
24—Aged 30	5/6/11	Tuberculous arthritis, no clinical symptoms of nephritis				

first hour This patient recovered and the nephritis completely cleared up in the course of a few weeks

CASE 2.—A patient, with scarlatinal nephritis, was in bad clinical condition at the time of the first test He had scanty urine of high specific gravity, smoky from blood and containing much albumin and many casts The prognosis seemed bad

The usual phthalein test was administered, the drug appearing in the urine in twenty-two minutes and only 4 8 per cent being excreted in one hour Three weeks later, the nephritis having almost disappeared and the clinical

TABLE 7.—PARENCHYMATOUS NEPHRITIS

Microscopical Findings	Per Cent of Drug Excreted in		Remarks
	One Hour	Two Hours	
Numerous casts	14,2		Ureters catheterized and equal amounts from each side
Casts	16 6		Impossible to increase urinary secretion by forcing water
Casts	14 0	32 0	
Casts	25 0	41 0	
Casts	21 1		
Casts	20 8		
Casts	30 3	52 5	
Numerous casts, R B C	11 9	26 6	
Casts	52 5		
	4 4	10 0	Died of uremia two months later
			Given 30 mg, but output not estimated
Few casts	20 2	42 2	
Casts	23 8	40 4	
Few casts	2 9	6 2	Died 11/16/10 Autopsy Severe amyloid nephritis, syphilitic, general amyloidosis
		Trace	
Casts	23 8	40 4	
Casts	7 5	18 9	Recovered, reports herself feeling well at present except for edema (April 1, 1911)
Casts		20 4	
Casts		33 0	
Casts		47 0	Left hospital in fair condition, but albumin (6 gm per liter) and casts were still present
Casts	33 3	51 6	
Casts		31 0	
Casts		22 0	
Casts		23 7	
Casts		43 1	
Casts		52 7	
Few casts	53 0 Subcut	61 6	The excretion for first half hour after intravenous injection is below normal
Few casts	54 4	*47 6	
Few casts		51 0	
Many casts	2 0	30 0	
Casts, few	14 3	24 3	Symptoms for six years, only in winter
Casts	No drug in 4 hrs		Died two days later in uremia No autopsy
Numerous casts	6 9		Developed erysipelas and following this an empyema which was
Numerous casts		16 6	drained Died 4/10/11 Autopsy Large white kidneys, subacute peritonitis
Few casts	36 7		Albumin and casts discovered accidentally
Few casts	Subcut inj 51 0		
Numerous casts		30 6	Voided freely after admission, edema disappeared in a few days Discharged 4/18/11
Few casts		66 6	Left hospital in a few days, felt perfectly well, albumin and casts still present
Many casts	54 9	66 8	Clinically this case is considered to have a good prognosis
Some casts	32 3	57 8	No symptoms of nephritis; albumin and casts discovered on routine examination

* Half hour test

condition being greatly improved, as well as the condition of the urine, the test was repeated, showing the appearance of the drug in seven minutes and an excretion of 38 1 per cent for one hour Six weeks later the patient was entirely well and excreted 50 per cent of a 30 mg dose in the first hour

CASE 3 —A boy of 7 years had a nephritis of obscure nature associated with purpura hemorrhagica and profuse hematuria The time of appearance of the phthalein was not obtained, but the patient excreted 19 4 per cent in the first hour and 19 1 per cent in the second hour Death occurred suddenly five days later from a suspected internal hemorrhage No autopsy could be obtained

CASE 4 —A boy, aged 8, was admitted with typical acute nephritis of a severe grade, the prognosis being considered unfavorable The phthalein output on admission was 11 per cent for two hours Four days later the clinical condition was much better and the phthalein output had increased to 28 4 per cent for two hours Two weeks later the nephritis had practically cleared up and the phthalein excretion increased to 68 8 per cent for two hours

CASE 5 —The patient, J , aged 35, was well until a few weeks before admission (May, 1910), when he developed dyspnea and marked edema Marked anasarca, low urine output, high specific gravity large amount of albumin and large number of casts were present The heart was normal There were no signs of uremia The phthalein test, given subcutaneously, showed 20 per cent excretion for two hours The clinical condition became gradually worse The patient died one week later without a second test

The autopsy showed slight chronic diffuse nephritis with marked acute diffuse nephritis

While no conclusions can be drawn from five cases, it is suggestive that in none of them was there increased permeability, but that on the contrary the permeability was markedly decreased when the condition was considered clinically grave In some of the cases below, classed as chronic nephritis, an acute exacerbation was associated with the chronic nephritis at the time of the test Here also the permeability was decreased but with the subsidence of the acute process the permeability increased

It should be remembered, however, that when an acute process is present, variations in function may be very rapid and that a good elimination on one day may be followed within a day or two by a marked decrease in function and *vice versa* Consequently, in cases of this type the test should be repeated frequently

CHRONIC PARENCHYMATOUS NEPHRITIS

In all, twenty-five cases belonging to the so-called type of parenchymatous nephritis have been studied These cases represent different grades of severity and the duration of the disease varies from a few weeks to seven years Details concerning these cases are seen in Table 7

In five very mild cases of short duration showing only slight edema, with albumin and casts, but with a normal urinary output, the time of appearance of the drug and the amount excreted was normal In one of these cases (No 5, Table 7) the time of appearance was eight minutes and the output 52 5 per cent for one hour Another patient (No 15) was a student who considered himself perfectly well but in whose urine albumin and casts were discovered by chance On close inspection a

slight edema about the eyes was detected No other evidence or suggestion of the disease could be found In this instance 53 per cent for the first hour and 8 6 per cent for the second hour was excreted following subcutaneous injection After intravenous injection 46 per cent was excreted for the first half hour (slightly decreased) and 17 per cent for the following hour and a half In three other cases a normal excretion was found but all three patients were free from symptoms, albumin and casts being the only indication of disease

In cases of longer standing or cases in which the disease is of ordinary severity the time of appearance has always been delayed slightly (from ten to twenty-five minutes) and the amount excreted is definitely below normal

In one patient (No 2, Table 7) who has been under constant observation for more than a year the time of appearance (twenty minutes) and the amount excreted for one hour (20 per cent) has remained practically unchanged Clinically his condition is better than a year ago

Another patient (No 14, Table 7—see also Chart 13), age 30, admitted Nov 25, 1910, with secondary lues and a definite parenchymatous nephritis of six months' duration showed an output of 47 per cent for two hours at which time his urine contained 50 gm albumin to the liter December 10 his phthalein output was 51 per cent and the albumin 25 gm to the liter, while his general condition showed but little change Because of the possibility of the nephritis being syphilitic in origin 0 45 gm of salvarsan was given intravenously December 26, his condition was definitely worse, urine decreased in amount and the albumin increased to 68 gm to the liter, the phthalein output dropped to 31 per cent January 3, his clinical condition was very grave, albumin 96 gm to the liter and the phthalein excretion was 22 7 per cent January 8, his condition was the same and the phthalein output unchanged On January 17, however, his clinical condition was improved albumin decreased in amount, and the phthalein output increased to 43 per cent February 7, the patient was again in good clinical condition, the albumin only 6 gm to the liter, while the output of phthalein increased to 52 7 per cent The blood pressure throughout ranged from 80 to 110 and no eye changes were present Although the phthalein output dropped *pari passu* with the exacerbation of the clinical manifestations yet at no point did it reach a level which would indicate an immediate danger whereas, clinically, death was considered imminent

Another interesting case (No 12, Table 7) is as follows

Mrs S, aged 57, admitted Nov 16 1910 with an acute exacerbation of a chronic nephritis Symptoms of mild uremia were present and the urine contained 7 gm albumin to the liter and many casts The systolic blood pressure was 190 mm Hg Her phthalein output was 19 per cent for two hours She gradually became more uremic and two weeks later was definitely comatose At this time her phthalein output was 20 per cent although her clinical condition was considered very grave In a few days she regained consciousness and shortly afterward left the hospital Ten weeks later the patient reported that with the exception of slight edema and dyspnea on exertion, all her symptoms had disappeared

In the most severe grades of chronic parenchymatous nephritis or where the disease is of long standing and associated with secondary

Name	Date	Clinical Condition	Time of Appearance (min)	Am't of Urine (cc)	S G	Albumin
1—M	12/ 6 /09		52			
2—F S, aged 71	2/ 1 /10	Arteriosclerosis, mild cystitis, fair condition		110	1,052	++
3—M, aged 48	1/27/10	Arteriosclerosis, hypertrophy of heart, emphysema	15	134	1,017	Alb 15 G to L
4—B, aged 55	2/10/10		15	45	1,020	Trace
5—S, aged 56	1/26/10	Arteriosclerosis	13	120	1,023	+
6—I L, aged 52	2/ 8 /10	Good condition	12	62	1,024	Trace
7—McC, aged 65	3/12/10				1,023	+
8—R, aged 51	1/28/10	Typhoid, 2d relapse, 3d month of disease		560	1,006	Transient
9—C, aged 39	3/31/10	Good condition	9	132	1,008	+
10—H, aged 55	1/13/10	Mild nephritis, good condition	8	470	1,006	+
11—K, aged 43 75401	11/ 7 /10	Arteriosclerosis, high blood pressure, 220 mm Hg		132		+
12—Mrs W, aged 21 75712	11/ 9 /10	Uremia, high grade choked disc, anemia severe		48	1,011	+
13—F G, aged 71 75711	11/ 9 /10	Arteriosclerosis, osteo arthritis, blood pressure 220 225 mm Hg		102	1,015	Trace of albumin found a few times
14—H, aged 65 75949	11/21/10	Arteriosclerosis, blood pressure 190 220 mm Hg		287	1,021	+
15—M M, aged 37 75999	11/29/10	Nausea, headache, anemia, blood pressure 215 mm Hg		130	1,008	+
	12/ 3 /10	Condition worse		34	1,014	+
16—J B S, aged 63 75918	12/ 3 /10	Cerebral arteriosclerosis, attacks of unconsciousness, blood pressure 180 200		104	1,022	+
17—A T, aged 69 76109	12/13/10	Edema, dyspnea, blood pressure 160-180		48	1,020	++
18—H G aged 36 76496	1/ 7 /11	Nausea and headache, hypothyroidism, blood pressure 110 125		127	1,012	Trace
	1/ 9 /11			110	1,009	Trace
	1/19/10			70	1,010	
	1/27/10			170	1,007	
19—Dr H, aged 40	12/31/10	No symptoms		165		+
20—C, aged 52	1/26/10	No symptoms		210		+
21—L M T, aged 60	2/ 7 /11	Nausea, headache, visual disturbances	14		1,008	+
22—D L O, aged 47 77449	3/24/11	Marked anemia, nausea, blood pressure 130, no edema		100		Trace
23—W T, aged 40 77268	3/24/11	Tuberculosis, osteomyelitis, persistent hiccough		150	1,015	+
24—L G, aged 12	3/28/11	Diagnosed on admission, diabetes insipidus, slight grade arteriosclerosis, blood-pressure 80 90 mm Hg		340	1,005	0
	3/31/11			430	1,005	0
25—S B G, aged 55	12/27/09	Slight headache, morning nausea, mentally clear, hypertrophy of prostate	40		1,012	Trace
	1/ 7 /10		30			Trace
Surg No 25174	1/10/10	Injection 30 mg phthalein	23			+
26—L, aged 50 7788'	4/25/11	Nausea, vomiting, blood pressure 190 mm Hg		120	1,020	Trace
27—D, aged 70	4/11/11	Cerebral arteriosclerosis, myocarditis, emphysema, blood-pressure 160-215 mm Hg		133	1,026	++
	5/ 7 /11	Bad clinical condition				++
28—F, aged 58	4/24/11	Dyspnea, arteriosclerosis, blood-pressure 170-200		360	1,010	+
29—Dr S, aged 45	4/10/11	Marked cerebral arteriosclerosis, blood-pressure 200 mm Hg		52	1,026	+
30—P, aged 55 77676	4/24/11	Arteriosclerosis and hypertension, blood pressure 170, attacks of unconsciousness, drowsy and oncoming uremia suspected		240	1,010	0 Trace on one occasion
31—W B, aged 50 77260	3/30/11	Arteriosclerosis, cerebral arteriosclerosis, chronic nephritis, blood pressure 185 240 mm Hg		45	1,020	0
32—H, aged 56	4/20/11	Marked eye changes, partially blind, blood-pressure 190 mm Hg, no edema, good physical condition	25	75		++
33—F	5/ 1 /11	Arteriosclerosis, hypertension, good physical condition				+
34—Dr G	5/ 1 /11	No symptoms except hyperacidity, gastric, trace of albumin and few casts for ten years				Trace

Microscopical Findings	Percentage of Drug Excreted in		Remarks
	One Hour	Two Hours	
			Excreted about 1 per cent for one hour, died in uremic convulsions two weeks later, no autopsy
Hyal and gran casts	34 5	48 3	
Numerous hyal and gran casts	23 7	40 3	
No casts	20 5		
Casts	3 0	18 1	
Gran and hyal casts	37 0		
Casts	21 7	35 7	
Occas casts	22 7	45 5	
No casts	31 0		
No casts	36 3		
Few casts		6 9	Died two months later, no autopsy, symptoms chronic uremia
No casts	0 0	0 0	Died 11/14/10 Autopsy Small granular kidneys with superimposed acute hemorrhagic nephritis
No casts	5 0	15 0	Died 11/15/10, of broncho pneumonia Autopsy (3461) Atrophy of right kidney from old renal thrombosis, left, small, granular kidney
Hyal and gran casts	20 0	33 1	
Few casts		11 6	Report 4/4/11 In bad condition, unable to get about, vomiting, headache, etc
Few casts		3 8	
Few casts	15 7	34 7	
Numerous casts		20 8	
Few casts		9 0	Discharged 10/7/11, feeling better, headaches and nausea some better
Few casts		6 9	
		4 6	
		8 0	
Casts	20 0	49 0	
Casts	18 5	38 5	
Numerous casts	5 0	6 0	Died, uremia, 4/17/11, no autopsy
No casts few R B C	0 0	0 0	Became drowsy, 3/27/11, died, uremia, 4/1/11, nephritis not suspected until test given
Casts		32 2	Died of tuberculous pneumonia, moderate grade of chronic nephritis
No casts		6 0	Trace of albumin found before admission, about 4/6/11, headache and trace of albumin and few casts in urine, died, in uremia, 1/10/11 Autopsy Extreme grade chronic interstitial nephritis
No casts		3 0	
0		Trace	Died in coma, 1/19/10 Autopsy Extreme grade interstitial nephritis, diffuse pyelonephritis
0		Trace	
		Trace	
No casts	0 0	0 0	Urea 15 per cent, catalase low died in uremia, 4/27/11
Casts		17 25	Catalase low
Casts		12 7	
Casts		38 1	
umerous casts		27 0	Craniotomy following operation became drowsy low urine output died uremic convulsions one week later, probably acute exacerbation of nephritis following ether anesthesia
Few casts		49 0	Some hematuria no uremic symptoms developed
Few casts		17 9	Had symptoms on admission of slight cerebral hemorrhage
Cast	2 0	8 0	Clinically considered very grave nephritis
No casts		50 0	
Numerous casts		51 0	Blood pressure not high considered clinically to have a very grave grade of nephritis

sclerotic changes, the output is reduced very markedly, and in some instances no trace of the drug can be found in the urine Here also, as in the interstitial type, the absolute failure of excretion, or the excretion of a mere trace, has been followed within a short time by death from renal failure Some details regarding a few of these cases may be of interest

Female, aged 28, admitted in August 1910 (Case 18, Table 7) History of edema of face for over two years Suffered some from headache For a few months previous to admission had been unable to work on account of general weakness On admission had nausea and occasional vomiting Mentally clear Marked anemia Some edema of face Urine contained large amount of albumin and numerous casts Output of urine small Phthalein test given and no trace of drug could be detected in the urine during the next three hours She gradually became more uremic, the nausea and vomiting becoming rather continuous although mentally clear Death occurred within four days No autopsy was obtained

Another case (No 10, Table 7), one of syphilitic nephritis, was of rather peculiar interest M A, aged 23 admitted Oct 24, 1910, exhibiting severe general anasarca and marked dyspnea Symptoms had existed for one month Pulse small and of low tension Some anemia No signs of uremia Heart was normal The urine had 6 gm of albumin to the liter but no casts were found Trace of sugar Some days after admission hyaline casts were discovered November 8, the albumin had increased to 30 gm to the liter, although the dyspnea was better and the general edema somewhat decreased The phthalein output was at this time only 6 per cent for two hours November 14, the general condition seemed about the same, but her phthalein output had decreased to a mere trace The following day she became suddenly irrational and rapidly went into coma and died within twenty-four hours Autopsy findings Syphilitic hepatitis, general amyloidosis, especially of kidneys and spleen, thrombosis of right renal veins and veins of left side of pelvis

Although the number of cases of chronic parenchymatous nephritis has not been very large, sufficient data have been collected to indicate that the test is of decided value in revealing the functional efficiency of the kidney in this condition In the mild cases very little disturbance of function is indicated and it may be impossible from the test alone to differentiate this condition from albuminuria unassociated with coarse renal lesions When there is a marked decrease in the phthalein output marked renal changes are present, and when only excreted in traces, or not at all, a grave prognosis should be given even though no signs of uremia exist

CHRONIC INTERSTITIAL NEPHRITIS

Twenty-three cases of the type clinically classed as chronic interstitial nephritis have been under observation (see Table 8) In many of these cases previous to the administration of the phthalein test no accurate idea of the degree of involvement of the renal function could be ascertained even after the most careful clinical study The phthalein test has proved itself of immense value in revealing the degree of destruction of the renal substance, and has demonstrated itself to be of extreme importance from the standpoint of both diagnosis and prognosis

In most of the cases of this series the time of appearance has been markedly delayed and the output of phthalein markedly decreased, where the output is lowest, the delay in appearance is most pronounced The time of appearance, however, is not so important as the amount of excretion Details of some of these cases demonstrate the accuracy of the phthalein test

S B G (No 25, Table 8) aged 55, surgical No 25 174 Admitted Dec 21 1909, complaining of difficult and frequent urination These urinary symptoms were dependent on prostatic enlargement, the residual urine amounting to 440 c c Patient was apparently in good physical condition, well nourished but slightly anemic Urine slightly cloudy, acid, specific gravity 1010 no sugar slight trace albumin and no casts Urinary output 2,000 c c in twenty four hours, urea ranging from 20 to 30 gm for twenty-four hours The phthalein test was given a faint trace appearing in forty minutes and at no time was more than the merest trace detected Repeated subsequent tests yielded always the same result One week after admission he began to exhibit signs of uremia, which gradually increased until deep coma ending in death supervened Autopsy Both kidneys presented marked atrophy, neither organ weighing one-third of normal, a severe grade of interstitial nephritis being present

This case is of particular interest because of the fact that the urinary output, the urea, the total solids and the total nitrogen were normal and casts were also absent

The following is a history of a case in which the diagnosis was perfectly apparent clinically but in connection with which the test proved a striking confirmation as the phthalein failed to be eliminated

Mrs W (No 12, Table 8), aged 21, admitted November 7, with symptoms of uremia Patient had had eclampsia in May, 1909, and had never fully recovered her former health Suffered from frequent attacks of epistaxis, dyspnea puffiness of eyelids and edema of ankles On examination marked emaciation and pallor was noted Red blood corpuscles 1,900 000, hemoglobin 22 per cent high grade of choked disk, blood-pressure 230, temperature normal Urine was somewhat decreased, specific gravity 1013 to 1019 albumin 1 9 gm to the liter, no casts acetone and diacetic acid positive at times

The phthalein test was given the day after admission and showed entire absence of elimination during two hours

Despite vigorous treatment coma became deeper and death supervened five days later

Autopsy (3460) showed an extreme grade of interstitial nephritis with a superimposed acute hemorrhagic nephritis

In the following case the diagnosis was exceedingly obscure until the evidence brought forward by the test was added Before the administration of the test, nephritis was only one of many possibilities entertained.

Mrs O (No 22, Table 8) aged 47 admitted March 23 1911 In October 1910 noted fatigue and dyspnea on slight exertion together with slight edema of lower extremities In December nausea and vomiting developed and have been present almost constantly since On examination patient was poorly nourished and showed marked anemia Red blood corpuscles 1 500 000 hemoglobin 15 per cent white blood cells 6 000 slight increase in cardiac dulness apex slightly

down and out slight systolic murmur in pulmonary area, no edema of extremities Urine pale yellow, specific gravity 1011, albumin—a trace, *no casts on repeated examination* Blood-pressure 135 Eye grounds negative Although nauseated the patient was mentally bright and seemed in no imminent danger The phthalein test showed no output in three hours Two days later the patient *became maniacal, dying within forty eight hours in uremic convulsions* No autopsy was obtained

Chronic nephritis can exist over a long period without recognition and may even exist in the absence of albumin and casts in the urine The following is another case illustrating the presence of nephritis in the absence of *positive clinical proof* and also the value of the phthalein test in revealing its existence

F G (No 13, Table 8) aged 71, who had had six previous admissions (for malaria febricula acute rheumatic fever and arthritis deformans) during the last five years, was again admitted Nov 7 1910 for edema of feet and legs vertigo and attacks of loss of consciousness Numerous urinalyses during these admissions failed to demonstrate any anomaly except a trace of albumin at one single examination An advanced arteriosclerosis and high blood pressure were recorded on previous admissions The chest was emphysematous the heart sounds distant Pulse 52 regular Blood pressure 220 Urine pale specific gravity 1012 acid albumin occasional trace, no casts Phthalein examination showed an output of only 5 per cent for the first hour and 10 per cent for the second indicating a severe grade of nephritis The next day definite signs of bronchopneumonia appeared and the patient died five days later

Autopsy (3461)—Atrophy of the right kidney as the result of an old thrombosis of right renal artery, *with chronic diffuse nephritis on the left side, small granular kidney*

The following case is an example of the difficulty encountered at times in differentiating clinically various forms of toxemias from true nephritis with uremia

S E (No 17, Table 8) aged 55, admitted Jan 3 1911 in a drowsy toxic condition, had a history of chronic bronchitis of long standing associated with dyspnea The present illness dated back two months, during which time the condition had become exaggerated Temperature was from 99 to 100 F Blood-pressure 160 mg The physical examination of chest revealed a bronchitis and some myocarditis The urine output was small, specific gravity 1030, acid, albumin 4 gm to the liter, hyaline and granular casts The physician in charge made a note saying "patient is certainly in uremia" and treatment for uremia was instituted A phthalein test, however, showed an output of 52 per cent for two hours which indicated a function not markedly impaired Some days later the temperature rose to 103 F and definite physical signs of a pneumonia became apparent Patient recovered from pneumonia but exhibited myocardial symptoms We have had another almost identical case of pneumonia in which the phthalein cleared up the diagnosis

The following case shows even more strikingly the ability of the phthalein test to reveal the presence of nephritis in the absence of any definite clinical evidence, being a case in which nephritis was not suspected before the administration of the test

L G (No 24, Table 8), aged 12 admitted March 27 1911, as an interesting case of diabetes insipidus The past history contained nothing of importance except that large quantities of urine had been voided for some time and he experienced marked thirst He was well nourished, not anemic and apparently a normal-looking boy His blood pressure ranged around 100 mm Hg Some thickening of the radial arteries was noted no definite eye changes The urine on admission was large in amount, from 2,000 to 2,500 c c clear specific gravity 1005-1010 *No albumin, no casts* At this time no suspicion of nephritis was entertained, although a trace of albumin had been noted once previous to admission The phthalein test, performed March 28, showed an output of only 7 per cent for two hours Three days later only 3 per cent was excreted With the exception of the phthalein findings absolutely no evidences of nephritis were present at this date A week later he developed headaches, and a trace of albumin in the urine appeared He rapidly became uremic and died, April 9 1911

Autopsy A most intense grade of chronic interstitial nephritis was present with almost complete disappearance of the cortex A slight grade of acute nephritis was superimposed

UREMIA

In twenty-five cases under study uremia has been present (see Table 9) In sixteen of these the uremia was grave, the patients exhibiting nausea, vomiting, drowsiness or coma and in several instances convulsions In the remaining nine, mild symptoms only were present and had persisted over long periods Eleven of the sixteen patients with grave uremia died during the attack *In all of these cases the phthalein elimination was zero or a faint trace only for two hours*

Of the five patients recovering from their uremia, in two instances the output was 20 per cent, the uremia being the result of an acute exacerbation of a chronic nephritis In two the output was 14 per cent, in both of these the uremia was precipitated by a double pyelonephritis The fifth case was an acute exacerbation in a case of chronic pyelonephritis in a man previously having had a nephrectomy This last patient has greatly improved but at present has a two-hour excretion of 13 per cent

In mild cases, exhibiting slight but persisting symptoms of uremia the excretion respectively was as follows 10 per cent in one, 7 per cent in three cases, a trace in one, 2 per cent in the other for two hours Four of the patients died within three months of the performance of the test Those living are still exhibiting evidences of chronic uremia four months having intervened in one instance

In five patients who did not exhibit uremia at the time of the test but in whom the phthalein output was below 8 per cent for two hours one excreting 6 per cent died within two months one excreting 3 per cent in one month, and the others are still living one after four months one after two months and the other after three weeks but all are at present exhibiting evidence of chronic uremia

In two patients (Nos 18 and 19 Table 9) not exhibiting uremia but with a markedly decreased phthalein output operation with long ether anesthesia in each instance was followed by uremia and death

Name	Date	Clinical Condition	Time of Appearance (min)	Amt of Urine (cc)	S G	Albumin
1—Miss S, aged 57 75881	11/29/10	Ac exacerbation of a chr nephritis, edema		80	1,009	++
	11/30/10	In uremia, drowsy		135	1,012	++
2—M A, aged 33 75555	11/ 6/10	Syphilitic nephritis, dyspnea		134	1,011	++
	11/14/10	Uremic		50		++
3—N K aged 13 75401	11/ 7/10	Blood pressure 220 had had suppression and slight drowsiness some days previous to test, no signs of uremia when test given		152		+
4—Miss W aged 21 75712	11/ 9/10	Nausea and vomiting, high grade choked disk, severe anemia		48		+
5—M M aged 37 75999	11/29/10	Edema, nervousness, headache, blood pressure 215		130	1,008	++
	12/ 3/10	Nausea and vomiting, decreased urine output		34	1,014	++
6—H G, aged 36 76196	1/ 7/11	Hypothyroidism nausea and headache, blood pressure 110 125		127	1,012	Trace
	1/ 9/11	Condition unchanged		110	1,019	Trace
	1/19/11	Hydrargyrism acute		70	1,010	Trace
	1/27/11	Better no nausea or headache		170	1,007	Trace
7—A T, aged 43	12/13/10	General anasarca, myocarditis, arterio sclerosis, mitral insufficiency, blood-pressure 160 220		96	1,010	59 to L
	12/19/10	Considered to have incipient uremia		96	1,012	+
8—G G, aged 28	7/11/10	Nausea, vomiting, chr parenchymatous nephritis		100		++
9—L M T, aged 60	2/ 7/11	Nausea, slight headache, chr interstitial nephritis visual disturbance	14		1,008	+
10—D L O aged 47 77449	3/27/11	Marked anasarca, nausea, blood pressure 130, no edema, chronic interstitial nephritis		100		Trace
11—S B G, aged 55 S 25174	12/17/09	Slight headache, nausea in morning	40		1,010	Trace
	1/ 7/10	Mentally clear, hypertrophy of prostate	30		1,010	
	1/14/10		23			+
12—M	12/ 6/09	Chr interstitial nephritis symptoms of uremia appeared one week after test				
13—F D, aged 37	1/ 3/11	Bilateral calculous pyonephrosis, nausea and vomiting		125	1,012	+
	1/ 7/11	Under hydrotherapy some improvement, nausea and vomiting better		125	1,022	+
	1/ 9/11	Still better		180	1,018	+
	1/11/11	Again more uremia		86	1,008	+
14—W J, aged 71	2/11/10	Carcinoma of prostate, double pyelonephritis, slight nausea	60	230	1,012	+
	2/18/10	Has nausea and some vomiting	50	159	1,012	+
	3/ 8/10	Much better, no nausea or vomiting	23	135	1,014	+
	3/18/10	Feels well, general condition excellent	16	252	1,014	
15—V W, aged 67 S 24958	11/14/09	Hypertrophy of prostate, septic temperature	30	*		
	11/24/09	Drowsy, temperature septic, uremic	38	†		
	12/15/09	Better, not uremic, evening temp 100 F	18	154	1,005	+
	1/21/10	Good condition	15	390	1,006	+
16—W, aged 45		Pyelonephritis of solitary kidney, vomiting and nausea severe		200		+
17—J, aged 35	4/10/11	In fair condition, no symptoms of uremia	25	225		++
	5/ ?/10	Acute nephritis, edema, small urine output, not uremic				
18—Dr S, aged 45 77672	4/11/11	Chr nephritis, marked cerebral arterio sclerosis, blood pressure 200 mm Hg, no signs of uremia				
19	4/15/11	Hypertrophy of prostate, moderate residual, history of uremic attack one year previously, given an intravenous injection of phthalein	7 3			
20—I S L aged 50 77883	4/25/11	Arteriosclerosis, chr nephritis, blood-pressure 190		120	1,020	Trace
22		Chr interstitial nephritis, blood-pressure 180-200, hemorrhagic retinitis, general anasarca, moderate nausea and vomiting		250	1,010	++
24—L G aged 12 77459	3/28/11	Diagnosed diabetes insipidus on admission, blood pressure 85, no sign of uremia		340	1,005	0
	3/31/11	Nothing to suggest nephritis		430	1,005	0 +
25—P, aged 27	12/10/10	Hypertrophy of prostate, pyuria	8			
	12/19/10	Has some fever, somewhat drowsy	23			

* No estimation, but twelve hours after injection phthalein was still being excreted

† Excreted 29 per cent in three hours and 40 per cent for six hours Urea, urinary output and total solids normal

Microscopical Findings	Percentage of Drug Excreted in		Remarks
	One Hour	Two Hours	
Numerous casts	7 5	18 9	Patient recovered in few days after last test
Numerous casts		20 4	Reports herself feeling well, edema still present
Few casts	2 9	6 2	Died 11/16/10, coma developed 11/15/10
Few casts		Trace	Autopsy Severe amyloid nephritis
Few casts	3 1	6 9	Died two weeks later, no autopsy
No casts,	0 0	0 0	Died 11/14/10 Autopsy Small granular kidneys with superimposed acute nephritis
Few casts		11 6	Report 4/14/11, in bad condition, unable to get about, nausea, headache, etc
Few casts		3 8	
Few casts		9 0	Discharged 2/7/11, headache and nausea better, died two months after leaving hospital with symptoms of uremia, nephritis was only regarded as a possibility in this case until phthalein test was performed
Few casts		6 9	
Few casts		4 6	
Few casts		8 0	
0		20 0	Patient left hospital in fair condition, uremia did not develop
+		29 4	
Numerous casts		0 0	No drug in four hours, died two days later in uremia
Numerous casts	5 0	6 0	Died in uremia 4/17/11
No casts few R B C	0 0	0 0	Became drowsy 3/27/10, died in uremia 4/1/10
0		Trace	Died 1/19/11 in uremic coma Autopsy Extreme grade chronic interstitial nephritis and diffuse pyelonephritis
		Trace	
		Trace	
	Trace		Died in uremic convulsions two months later, no autopsy
Cloudy from pus	0 0	0 0	Double nephrotomy done rapidly under gas 1/11/11 in hope of giving some relief, died in uremia within twenty four hours, kidneys were thin-walled pus sacs
Cloudy from pus		Trace	
Cloudy from pus		5 5	
Cloudy from pus		Faint trace	
Cloudy from pus	0 0	13 8	For three hours total excretion 33 per cent
Cloudy from pus	Trace	14 8	For three hours total excretion 27 3 per cent
Cloudy from pus	18 9	10 6	Perineal prostatotomy for removal of obstruction 3/21/10
	35 2	72 4	Still living 3/1/11
Cloudy from pus	8 5	35 5	Perineal prostatotomy 12/22/09, good recovery, still living, in good
Cloudy from pus	23 6	57 0	condition, 5/1/11
Cloudy from pus		5 0	
Cloudy from pus	6 0	13 0	
Numerous casts		20 0	Condition became worse and died in coma one week later
Numerous casts		27 0	Cranial exploration 4/14/11, following operation (ether anesthesia) was drowsy and had very low urinary output, died uremic convulsions one week later, probably acute exacerbation of his chronic nephritis
Some casts	§	¶	Prostatectomy under long ether anesthesia 4/16/11, suppression of urine at once, died 4/20/11, no autopsy
Casts	0 0	0 0	Urea 1.51, died in uremia two days later
Numerous casts	1 0	4 0	Died in uremic convulsions two weeks later
0		6 0	Trace of albumin found once prior to admission polyuria for two years about 4/3/11 headaches appeared 4/11/11 trace of albumin, died in uremia 4/9/11 Autopsy Extreme grade of chronic interstitial nephritis practically no renal cortex
0		3 0	
Pus	18 5	45 5	Died about ten days after last test of urea in no operation Autopsy
	8 0	13 0	Old chronic pyonephrosis of left kidney right kidney hypertrophied, showing chr diff nephritis and marked diffuse acute pyelonephritis

* Normal for from three to five minutes

¶ First half hour 25 per cent Normally this much excreted in less than ten minutes

§ Total excretion for one hour, 47 per cent

CARDIAC AND CARDIORENAL CASES

An attempt has been made to differentiate by means of this test between those cardiac cases with broken compensation and passive congestion of the kidney, associated with the presence of albumin and casts in the urine and those cases in which cardiac insufficiency is associated with varying grades of true nephritis In this connection thirty-three cases have been studied There were eighteen cases in which the *purely clinical diagnosis* was that of uncomplicated cardiac disease, and fifteen cases of cardiac disease associated with nephritis From a study of these cases there appears to be no doubt but that decrease in function accompanies marked passive congestion of the kidneys in the absence of any true nephritis As the cardiac condition improves, however, the passive congestion becoming less marked and edema subsiding, the output of phthalein increases, and in one case rose from 16 per cent to normal in the course of one week, the patient in the meantime losing seventy pounds in weight with the disappearance of a general anasarca

The opportunity of comparing the result of the phthalein test with the findings at autopsy was afforded in the following case

H B (No 76710), aged 29 admitted Jan 20, 1911, complaining of severe dyspnea and swelling of feet which had existed for two weeks only Physical examination revealed markedly increased cardiac dulness, mitral and aortic insufficiency, dilatation of the heart some ascites, bronchopneumonia, blood pressure 190, moderate grade of secondary anemia Urine high colored, specific gravity 1046, acid, albumin + + +, large number of hyaline and granular casts Phthalein test showed an output of 26 per cent for two hours Patient died on the day following admission

Autopsy Chronic mitral and aortic endocarditis, chronic myocarditis marked hypertrophy and dilatation of the heart, a moderate grade of chronic diffuse nephritis, with some superimposed acute nephritis Death in this instance was in great part due to cardiac failure

In those cases with broken compensation which presented a high phthalein excretion, in nearly every instance albumin and casts entirely disappeared with the improvement in the cardiac condition An example of this class is the following case

The patient, G W, presented a severe grade of general anasarca *with albumin* and casts in the urine at the time of the test He excreted 65 8 per cent of *phthalein in two hours* As the anasarca decreased, albumin and casts entirely disappeared, the kidneys showing no permanent injury from the break in compensation

The presence of a general anasarca, particularly when edema exists at the point of injection, probably introduces some error from the standpoint of absorption The extent of this error has yet to be determined From a study of these cases we feel that the phthalein test will prove of value in determining what degree of renal insufficiency exists in this class of disease

With improvement in the cardiac condition and the disappearance subsequently of edema a continued low phthalein excretion will indicate with considerable certainty the presence of permanent organic changes in the kidney We feel, however that a much larger series should be studied clinically and at autopsy before very definite conclusions can be drawn

TABLE 10—THE RELATION OF PHTHALEIN OUTPUT TO BLOOD PRESSURE, TO CHANGES IN THE EYE-GROUNDS AND TO THE BLOOD PICTURE

Patient	Eye Grounds	Syst Blood Pressure	Red Cells	Hb Per cent	Phthalein Output Per cent
Mrs Y	At present normal	220 280			32
Henry B		190	3,200,000	60	26
Fr C	Normal	120			55 5 1 hr
I B	Normal	100-125	4 040 000	75	36
G W	Normal	85 115	4,000 000	75	65 8
L E S	Normal		4,800 000	70	48
F X S	Normal	210	3,300 000	91	40
S R		180 210			33 3
G P		155-170	5 000 000	90	22 7
P		210	4 000 000	75	15
L W T		95 125			54 3
S W	Normal	140-190	4 200,000	70	30
R	Choked disk	160 218	4 500 000	85	52
R S		135 170	4 900,000	68	35 7
C B		80 130	5 100 000	98	44 4
J J		80 110	4,800 000	80	71 5
F K	Hazy disks, white splotches and tortuous vessels	130 180	4 700 000	50	27 5 33 3
H G		80-120	4 200 000	70	6 66
K	Edema of disks	80-110	5,000,000	105	17 22 17 52
J S		106 210	2 700 000	42	20
J S		180 220			31 7
Mrs O	Negative	130	1 500 000	15	0
A T	Normal	160 180	4 500 000	78	20 8
W K		170 215	4,700 000	98	5
L W			2,500 000	30	60 9
H G	Negative	110 140	4 200 000	62	3 8
M A	Negative	100 120	3 400 000	55	1
G H	Dim outline old hemorrhagic retinitis	190 220			33
P S	Negative	90 110	5 200 000	91	60 4
C N		90 170	5 600 000	80	26 3
J F	Negative	120 150			62 6
R D	Negative		5 300 000	95	65
Mrs W	Choked disk	230- 80	1 900 000	22	0
A T	Normal	160 210	4 500 000	71	20
G P	Normal	100 180	5 000 000	71	25
F G	Normal	220 235	4 500 000	80	15 5
S E	Normal	160			50
T E	Normal	85 100	3 200 000	50	0
M M		215	5 200 000	75	11 3
B		220			40

MISCELLANEOUS CASES

A large number of miscellaneous medical diseases have been also studied from the standpoint of phthalein excretion among the number being ten cases of lobar pneumonia Two of these cases had hyal-

dences of a mild nephritis during the attack, which was associated with a definite decrease in phthalein output In both cases the urine was entirely normal one month later, as was also the phthalein output In pneumonia the output is little if any decreased and bears no relation to the chlorid excretion

Three cases of persistent albuminuria have shown a normal output In no disease other than renal, so far studied, has marked reduction of the phthalein excretion been encountered

THE RELATION OF PHTHALEIN OUTPUT TO BLOOD-PRESSURE, TO CHANGES IN THE EYE-GROUNDS, AND TO THE BLOOD-PICTURE

In the majority of cases of chronic nephritis in which the blood-pressure has been high, the phthalein elimination has been markedly decreased, but no exact parallelism exists inasmuch as not a few instances have been encountered in which the systolic pressure has been over 200 mm Hg and the phthalein output one-half of normal, while, on the other hand, there have been instances in which the blood-pressure has been normal while the phthalein output has been zero or nearly so, the patients shortly afterward dying in uremia While a high blood-pressure when present is considered of diagnostic and prognostic value taken in conjunction with other clinical data, yet many patients died of renal insufficiency and exhibited a blood-pressure which was normal or practically so Nor is the blood-pressure, even when high, increased in inverse proportion to the decrease in renal function

While in some instances marked changes in the eye-grounds, choked disk, tortuous vessels, hemorrhages, etc have been present coincident with a very low phthalein output, in many cases even of the most advanced and even fatal nephritis, no changes whatever in the eye-grounds could be detected, the patient at the same time failing to eliminate the phthalein

Moderate or rather severe grades of secondary anemia in the absence of disease of the kidneys can be present without any diminution in the phthalein elimination, for instance, two patients, one with 2,500,000 red cells and hemoglobin 30 per cent, the other with hemoglobin 30 per cent, eliminated 61 and 57 per cent, respectively, for two hours A dog, with a red count of 7,290,000 and a phthalein output of 41 7 per cent for one hour, was bled 120 c c, resulting in red count of 5,400,000 and no change in phthalein excretion

VALUE OF TEST FROM A SURGICAL STANDPOINT

Through the encouragement of Dr Young we have been enabled to study the phthalein excretion in a large series of cases of urinary obstruction, in order to determine the value of the test in revealing the func-

tional capacity of the kidney in these cases This is a consideration of grave importance in this connection, since the development of uremia or renal failure has been responsible for a great part of the mortality following surgical interference

As a result of obstruction in the lower urinary tract, pathological changes may occur in the ureters and kidneys, dilatation of the ureters, varying grades of hydronephrosis, and, as a result of the continued high pressure, atrophy of the parenchyma of the kidney Not infrequently infection occurs with the development of a pyelitis, a diffuse or localized pyelonephritis, or pyonephrosis The occurrence of these complications is often difficult of recognition and is often overlooked, particularly in the absence of symptoms of renal inadequacy A large proportion of these cases of urinary obstruction have cystitis associated with albuminuria The presence of casts in the urine is no contra-indication to operation The urinary output may be normal in many instances, also the urea and total solids, and yet the patient may be on the verge of renal failure and disastrous results may follow surgical interference

The test has been used in at least 150 cases of urinary obstruction, mostly cases of prostatic hypertrophy The technic involved in these cases necessitates the use of a catheter, otherwise it does not differ from that described above For a detailed consideration of the value of this test in relation to obstruction in the lower urinary tract, see our previous publications on the phthalein test [36]

In the majority of cases the test indicates more or less of renal impairment, and taken in conjunction with the clinical condition it is of more value than the study of urine output, total solids, total nitrogen and urea estimation combined

A marked decrease in the amount excreted invariably means severe derangement of renal function, which may be of either a temporary or permanent character Under such conditions one should proceed with extreme caution and no surgical intervention should be attempted without further study together with preliminary treatment This preliminary treatment as introduced some years ago into this clinic by Dr Young consists of drainage by means of a retention catheter or frequent catheterization, together with the administration of large quantities of water

Under this regimen repeated functional tests will demonstrate eventually the nature of the derangement for in true interstitial nephritis the output will continue low, whereas if the derangement is purely functional or secondary to pyelonephritis usually improvement will follow as a result of the treatment and will be indicated by a decrease in the time

36 See Reference 2 and also Ann d mal d Org Gen Urin, February and March 1911, and Tr Am Assn Gen-Urin Surg 1910

of appearance of the drug and simultaneously an increase in the amount eliminated

The functional derangement due to infection in these cases is a much more dangerous condition than is the presence of even a fairly advanced condition of interstitial nephritis The use of the test enables one to select a favorable time for operation In cases exhibiting a continued suspiciously low output the use of nitrous oxid gas or spinal anesthesia is suggested as preferable to ether in order to protect the kidneys When only a trace of the drug continues to be excreted, operation should not be attempted at all except in an emergency, even though the patient presents no evidence of uremia

In our original paper[2] we stated that a dropping phthalein output was a contra-indication to operation except in cases of necessity This decrease in function usually means some change in the renal condition and in most of our cases it has been caused by the development of a pyelonephritis or an exacerbation of an old process It is obviously wise to wait until the kidneys have recovered from this acute shock before subjecting them to further injury through operation

URINARY OBSTRUCTION

As regards the amount of excretion, below which one should not operate, we do not attempt to draw a definite line The test simply indicates the renal function and it depends on the operator what risks he is willing to assume, the probabilities of fatality increasing as the phthalein output decreases We do however recognize when we have low function which otherwise may be unrecognized and have found that preliminary treatment in most instances, whether it be by suprapubic, perineal or catheter drainage allows a regeneration of function which will be indicated by the test and enables the patient later to undergo the graver operation of prostatectomy with less risk

The test can be used to equal advantage preliminary to any surgical procedure where it is deemed important to know the true functional capacity of the kidneys

TECHNIC OF THE PHTHALEIN TEST AS APPLIED TO ESTIMATION OF THE FUNCTION OF THE INDIVIDUAL KIDNEY

Functional tests have already demonstrated their great value in this connection But they have at most been able to determine only the relative working capacity of each kidney and have shed very little light on the absolute functional capacity of each organ

The phthalein test in association with ureteral catheterization has been used in seventy-five cases of unilateral or bilateral disease (Table 11), the technic being as follows In most of these the subcutaneous administration was used Recently, however, the intravenous method of adminis-

tration has been employed, whereby the time necessitated for observation has been reduced to half an hour, collections being made at fifteen-minute intervals Where it is desirable to determine whether the supposedly healthy kidney can assume sufficient function to permit of the removal of the other kidney, only a half-hour period of observation is necessary

For the particulars concerning the technic of application of the test in association with ureteral catheterization, see our original publication [2]

RESULTS OBTAINED WITH THE PHTHALEIN TEST IN UNILATERAL AND BILATERAL DISEASE OF THE KIDNEY

In normal cases the time of the appearance of the drug from the two sides has been almost always the same and in the majority of cases this has been five to ten minutes following subcutaneous and three to five minutes following intravenous injection The time of appearance of course, will vary somewhat with the rate of urinary secretion Normally the amount excreted by each kidney will be practically the same

The series of cases studied include tuberculous or pyogenic infection unilateral or bilateral, calculi, hydronephrosis hypernephromata etc [1]

When one kidney only is diseased the time of the appearance of the drug is delayed on the diseased side and the amount excreted is not only relatively but absolutely decreased The amount of delay in the time of appearance is comparatively of little value Reliance is to be placed only on the quantity excreted during a period of one-quarter one-half or one hour, depending on the method of administration

Although in the majority of these cases of unilateral disease the combined output is equal to that of two normal kidneys the greater part of the excretion is shown to be performed by the healthy kidney In proportion to the decrease in function on the diseased side, approximately there is a proportionate increase in the function on the healthy side In such cases following nephrectomy the remaining kidney eliminates after the lapse of two or three weeks, an amount of drug which is normally excreted by two healthy kidneys In all cases studied, the output from the remaining kidney has been greater than the combined output from the two kidneys prior to operation

While the total urea from the combined urine is no true index of the functional activity of the kidneys the comparative urea output from each kidney is of decided value The same amount of urea is presented to each kidney for elimination and therefore it is possible to determine to some extent the proportionate amount of work which each kidney is performing Barringer has pointed out that when the output from one kidney is four times as great as that from the other it is safe to [illegible]

[1] He details concerning forty-two of these cases [illegible] communications Tr Am Assn Gen Urin Surgeons 1911 [illegible] Org Gen urin February and March 1911

Number of Case and Name of Patient	Date	Diagnosis	Amt of Drug Given in mg	Time of Appearance (min)	Amt Urine, C c	Reaction of Urine
43—Mrs L	11/8/10	Previous operation for right ureteral stricture	6	L R	330 0 215 0	++
44—E	11/16/10	Tuberculosis of bladder and left kidney	6	L 30 R 10	17 0 19 0	++
45—G K	11/10/10	Calculi right kidney	6	L R	170 0 190 0	++
46—P	11/22/10	Tuberculosis of right kidney	6	L 8 R 10	34 0 55 0	++
	12/23/10	Total function			70 0	
47—B	12/6/10	Tuberculosis of both kidneys	6	L 8 R 8	138 0 88 0	++
	12/14/10	Total function Nephrectomy 12/15/10				
	12/20/10	Excretion of remaining kidney				
	12/26/10	Excretion of remaining kidney				
48—Mrs Z	12/7/10	Right nephralgia, pelvic cap 25 c c	6	L R	150 0 150 0	++
49—L	12/10/10	Left nephroptosis, pelvic dilatation 18 c c	6	L 8 R 8	53 0 53 0	++
50—E M	12/16/10	Calculi left kidney, one calculous ureteropelvic juncture	6	L 16 R 11	17 5 24 5	++
51—K	12/25/10	Calculous pyelonephritis, left	6	L 15 R 8	61 0 86 0	++
52—B	12/27/10	Tuberculosis left kidney	6	L ? R 8	30 0 59 0	++
	1/13/11	After nephrectomy function of remaining kidney	6			
53—Dr B	12/30/10	Slight infection left kidney, previous nephrolithotomy	6	L 8 R 7	66 0 109 0	+−
54	1/6/11	Slight pelvic dilatation right side	6	L R	70 0 65 0	++
55—W	1/7/11	Multiple abscesses left kidney, gonorrheal	6	L R	125 0 210 0	+
56—B	1/9/11	Tuberculous pyonephrosis right side	6	L R	240 0 ?	+
	5/10/11					
57—O	1/20/11	Hypernephroma right side	6	L 10 R ?	200 0 85 0	++
58—G	1/26/11	Left renal calculus	6	L 13 R 8	66 0 27 0	++
59—G	1/28/11	Calculus lower end left ureter, marked hydronephrosis	6	L 40 R 10	7 0 15 0	++
	1/31/11					
60—H	2/4/11	Nephroptosis left side	6	L 13 R 15	115 0 125 0	++
61—Mrs A	2/21/11	Probable double pyelonephritis, subacute	6	L R		++
62—A	2/10/11	Enormous hydronephroses of left kidney, 900 c c		L none R 15	900 0 30 0	+
63—H	1/18/11	Double pyelonephritis (No 6 catheter used on left side, No 8 on right)		L 13 R 15	90 0 240 0	
64—C	1/13/11	Slight infection of right kidney, possible stone		L 7 R 8	11 0 11 0	
65—C B	3/29/11	Persistent fistula of left ureter following ureteral lithotomy		L 30 R 20	40 0 108 0	
66—G	5/10/11	Nephroptosis left side and hydronephrosis		L R	10 5 14 0	
67—K W	5/5/11			L R	210 0 350 0	
68—C	3/29/11	Multiple renal calculi, right side		L 5 5 R	85 0 13 0	
69—G	5/10/11	Slight pain in right renal region, few pus cells in bladder urine (Second, 15 minutes)		L 5 R 9 L 4 8 R 6 5	3 8 3 8	(15 min) (15 min)

* Forty two cases not shown in this table will be found in previous publication
† Acid reaction indicated by plus, alkaline, by minus

Chemical and Microscopical Findings	Percentage of Drug Excreted	Urea in Cg	Remarks
Clear	21 0	66 0	
Clear	17 0	21 5	
Pus and tubercle bacilli	2 0	10 0	Left collected transvesical, nephrectomy, badly diseased kidney, recovery
Clear	34 0	32 0	
Cloudy, pus cells and cocci	15 0	57 0	Nephrotomy, lower one-third kidney filled with calculi, upper two thirds normal, recovery
Clear	20 0	68 0	
Clear	26 0	68 0	Nephrectomy 12/5/10, recovery, 12/7/10, 32 per cent excreted one kidney one hour, 12/13/10, 28 per cent excreted one kidney one hour, 12/20/10, 50 per cent excreted one kidney one hour
Cloudy, pale, pus cells few tubercle bacilli	17 0 45 0	44 0	
Slightly cloudy, pus cells, tubercle bacilli	26 0 12 0	96 0 55 0	Leakage of 27 c c with 6 per cent urea and 3 per cent phthalein, probably from left as small catheter used on this side, nephrectomy, right side, recovery, kidney badly diseased
Slightly cloudy, pus cells, tubercle bacilli	38 0 28 5 50 0		
Clear	18 0	45 0	Suspension, cure
Clear	19 2	22 5	
Clear, negative	15 2	61 0	Suspension, cure
Clear, negative	19 2	84 8	
R B corpuscles, no pus cells or bacteria	9 0	31 5	Nephrolithotomy, cure
Clear, no pus cells or bacteria	28 0	68 6	
Cloudy, pus, bacilli	10 0	36 6	Nephrectomy, recovery
Clear	22 0	86 0	
Cloudy, pus, bacilli	2–3	20 0	Nephrectomy, recovery, left collection transvesical
Clear	39 0 43 0	70 8	
Hazy, cocci, no pus cells, trace albumin	20 0 36 0	42 9 68 1	No operation
Clear, no albumin			
Clear	26 0		Suspension
Clear	25 0		
Cloudy, pus	12 5		Nephrectomy, recovery
Clear	40 0		
Albumin	16 0		Nephrectomy, recovery, left collected transvesical
Pure, pus	0 0		
Function remaining kidney, collection 1 hr, 10 min	17 0		
Clear	44 0	100 0	Nephrectomy, death, fourth day, from hemorrhage slight traces of right kidney only, almost entirely neoplastic
Bloody	Trace	25 5	
Red blood corpuscles, few leukocytes	13 0	39 6	Nephrolithotomy, cure
Clear	27 0	64 8	
Clear, few leukocytes	1 0	2 8	Removal of calculus, recovery
Clear	21 0	21 0	
Total fuction without catheterization	50 0		
Clear, no pus or bacteria	15 0		No operation
Clear, no pus or bacteria	18 0		
Clear, few pus cells	14 0		Nephrectomy, right side, congenital atrophy kidney with diffuse cortical infection, death sixth day, from pneumonia
Clear, few pus cells	1–2		
Blood (old)	0 0		Nephrectomy, large, thin walled sac removed
Clear	33 5		
Pus cells and cocci	5 2	90 0	Leakage 210 c c 1 5 per cent urea and 10 2 per cent phthalein leakage from left side probably
Pus cells and cocci	9 0	32 0	
Cloudy no pus red blood-corpuscles or bacteria	27 0		
Pus bacilli and cocci	21 0		
Cloudy, pus cells	1 0	20 0	Nephrectomy, recovery, kidney showed severe old pyelonephritis
Clear pale	27 0	108 0	
Clear	Trace	13 0	
Clear	15 0	29 0	
Clear	15 8	100 6	Total function next day without catheter 45 per cent
	12 8	100 ,	
	69 0		45 per cent for one half hour
Clear	0 0		
Clear	23 0	6 7	Kidneys are apparently normal
Clear	22 0	9 7	
Clear	11 0	8 6	
Clear	10 7	1 , 0	

the diseased kidney provided that the urine from the opposite side gives no indication of disease It is of most value when there is a marked disproportion from the two sides This test, however has its failings, as this proportion does not always exist Again, the urea determination *indicates only the relative amount of work that each kidney is performing,* and as the exact amount of urea present in the blood is not known, the test shows only the relative activity of each kidney and not their absolute functional activity

Again it affords no indication as to whether the kidney is working at its ordinary capacity or as to whether the reserve force is called on and the kidney is working at its maximum, and therefore unable to withstand any additional strain

The inefficiency of these methods has necessitated the introduction of the more recent methods of estimating the functional ability

A striking parallelism exists between the relative amounts of phthalein excreted and the relative urea output for any period but the phthalein has an additional advantage inasmuch as it indicates not only the relative excreting capacity of the two kidneys, but furnishes an approximate idea of the absolute capacity of each kidney

In all seventy-five cases of unilateral or bilateral renal disease have been studied in conjunction with ureteral catheterization the series comprising cases of renal calculi, renal tuberculosis, non-tuberculous infection hypernephromata, hydronephrosis and nephroptosis ureteral calculi ureteral strictures hematuria cases of polycystic kidney and a few miscellaneous cases

In bilateral disease it has been found possible to determine the individual function (absolute or relative) of each kidney It is in this class of cases particularly that the shortcomings of other functional tests have been most apparent, as one kidney may be doing twice or three times the amount of work of the opposite kidney and still be unable to assume the additional work of the other kidney It may be doing the major part of the work at the expense of all or nearly all of its reserve power, but the phthalein test determines whether the kidney has a functional capacity which is normal, less than or greater than normal and to what degree In two cases of double renal tuberculosis in which the amount of pus from each side was practically the same, the test permitted it to be determined that in each instance one kidney had a function greatly in excess of the other, indeed sufficient functional capacity to allow of successful nephrectomy, marked improvement in general condition occurring subsequently in each case

The details of one of these cases are worthy of report

B, aged 35, admitted Dec 4 1910, complaining of pyuria and some failure in general health

Cystoscopic examination revealed a normal bladder Separated urines yielded the following finding

Left	Right
138 c c	88 c c
Cloudy	Cloudy
Pus cells	Pus cells
Tubercle bacilli	Tubercle bacilli
Albumin +	Albumin +
Urea 96 cg	Urea 55 cg
Phthalein appeared in 8 min	Time of appearance 8 min
26 per cent for one hour	12 per cent phthalein

Leakage of 27 c c —3 per cent phthalein and 14 cg of urea

Although disease existed on both sides and from the character of the urine it was impossible to determine which side was more badly diseased, the phthalein indicated that the left kidney, although diseased, had the function of a normal kidney The right kidney in this case was evidently the primary seat of disease Nephrectomy of right kidney was successfully undertaken, being followed by a marked improvement in the patient's general condition

The function of the left kidney gradually increased until the output at the end of three weeks was 50 per cent, equal to that of two normal kidneys The kidney removed was badly diseased

It seems probable that in this case the infection was limited to a localized area and that the greater part of the kidney was healthy and subsequently was able to undergo compensatory hypertrophy

In a case of bilateral pyonephrosis due to calculus, striking confirmation of the accuracy of the findings of the test was afforded by the following case

T E, aged 37, admitted Jan 1, 1911, with vomiting and pain in epigastrium Diagnosis double renal calculi and pyonephrosis, uremia In 1903 patient had right renal colic for first time, following which he passed two stones Since then he had had two similar attacks on the left side For last three months he has had frequent attacks of pain on the left side, dyspnea, vertigo and vomiting

On examination patient was found markedly emaciated, hemoglobin 50 per cent red blood corpuscles 3,300,000, white blood cells 18 500 Kidneys not palpable no tenderness X-ray showed stones in both kidneys and in upper portion of left ureter Urine 1700 c c in twenty four hours, specific gravity 1017, albumin + + and cloudy from pus

Phthalein test January 2, no drug for two hours Under forced water the urinary output increased and patient became less toxic nausea and vomiting disappearing Phthalein output was now 5 per cent Two days later uremic symptoms reappeared and the phthalein output was again zero A double nephrotomy under gas was rapidly done in the hope that some relief might be thus secured Both kidneys were found to be merely thin walled sacs filled with calculi and pus Patient died in uremic convulsions in less than twenty-four hours

The existence of an infantile kidney may be readily overlooked inasmuch as under normal conditions the urine from such a kidney may be absolutely normal so far as color specific gravity and urea percentage are concerned The literature abounds with numerous reports of death from renal failure following nephrectomy due to the inability to recognize

the presence of an infantile kidney Recently, Kummel[37] and McArthur[38] have each reported deaths following nephrectomy where an infantile kidney had been left to assume the work In our series two such kidneys, the seat of disease have been removed, and in a third case with bladder tuberculosis and suspected renal tuberculosis without localizing symptoms on either side, an exploration of the left kidney revealed a healthy but infantile kidney Exploration was necessary inasmuch as the bladder was markedly contracted and it was found impossible to catheterize the ureters A similar condition was encountered in a cat utilized in our experimental work (described below)

The details of one of these cases is presented

C, admitted March 19 1910 Tuberculosis in an infantile kidney The left ureter was catheterized but on account of ulceration of the right ureteral orifice it was found impossible to catheterize this ureter, the urine from this side therefore being collected transvesically The separated urines were as follows

Left	Right
40 c c	20 c c
Clear	Slightly cloudy
Normal	Some pus cells, no bacteria
Acid	Acid
Specific gravity 1020	Specific gravity 1016
Urea 28 per cent	Urea 18 per cent
Total urea 112 cg	Total urea 34 cg
Phthalein appeared 6 min	Phthalein appeared 18 min
Phthalein excreted 44 4 per cent	1 per cent excretion

The right kidney was removed and was found to weigh 40 gm The upper two fifths were destroyed by tuberculosis

When the disease is present in the large kidney nothing short of functional test will reveal the presence of the infantile kidney

In certain cases owing to malformation or strictures in the lower end of the ureters, and especially in bladder tuberculosis it may be possible to catheterize one ureter only When infection of the bladder exists microscopical and chemical examination of the urine collected transvesically is obviously unreliable as an indication of a healthy or a diseased condition of the uncatheterized side It is therefore necessary to resort to estimation of functional capacity in order to determine the presence or absence of disease on the side not catheterized

In many instances of tuberculosis, as in the following case, it is the healthy kidney which can be catheterized and the absolute evidence of disease on the other side in the presence of an infected bladder must be ascertained, not by microscopical examination of the urine but by functional capacity

Diagnosis Tuberculosis of right kidney and stricture of lower end of ureter Patient admitted with history of attacks of pain in the right kidney region and

37 Kummel Jour Surg, Gyn and Obst, April, 1911
38 McArthur Jour Surg, Gyn and Obst, April, 1911

an intermittent pyuria A skiagram was negative, the bladder urine was clear but microscopically contained a few leukocytes, no organisms Cystoscopy revealed a normal bladder The left ureter was readily catheterized but an obstruction at the lower end of the right ureter obstructed the catheter on this side, necessitating transvesical collection The separated urines were as follows

Left	Right
45 c c	70 c c
Acid	Clear
Clear	Few leukocytes
Specific gravity 1024	No organisms
Urea 65 cg	Acid
Phthalein appeared in 12 min	Specific gravity 1004
32 per cent excreted	Urea 19 cg
	Phthalein appeared in 20 min
	5 per cent excretion

On account of the low function and the presence of the ureteral stricture, a probable diagnosis of tuberculosis of the right kidney was made and a nephrectomy performed On examination this kidney was found to be badly diseased although the urine contained no pathological features

Occasionally it is impossible to catheterize either ureter, particularly in marked vesical tuberculosis Here by the aid of indigocarmin noting the time of the appearance of the drug on each side and from the evidence obtained from cystoscopy and from localizing clinical symptoms, it will generally be possible to arrive at a probable diagnosis as to which kidney is involved The total function as determined by means of phthalein will determine whether the disease is unilateral or bilateral When one kidney is suspected and yet a good total renal function has been indicated this side can be explored and if found to present evidence of marked disease can be removed with safety without exploration on the opposite side Obviously excretion of a large amount of phthalein must have been performed by the opposite kidney Such a case is here recorded

The patient had marked vesical symptoms and pyuria with tubercle bacilli in the urine On cystoscopic examination the whole trigone was badly inflamed and edematous The right ureteral orifice was badly ulcerated and could not be catheterized An attempt to catheterize the left side also failed on account of the edematous condition of the mucous membrane and the contracted condition of the bladder This cystoscopic picture of the right ureteral orifice indicated probable disease of this kidney but disease of the opposite side also could not be excluded A phthalein test for total function showed in excretion of 15 per cent for one hour A right-sided exploration revealed an advanced tuberculosis of this kidney and a nephrectomy was performed without exploration of the other side which must have been responsible for the good renal function indicated by the test The recovery was uneventful

A patient showing right-sided intermittent hematuria and chronic nephritis admitted Sept 19 1910, had ureters catheterized and the separated urines yielded the following data

Left	Right
13.5 c c	16 c c
Acid	Clear
Bloody	Acid
Urea 18 cg	21 cg urea
Phthalein 11 min	Appeared 11 min
11 per cent. excreted	11 per cent excreted

The following day total function without catheterization was studied, output being 22 per cent The equal and decreased function as indicated by the phthalein showed a bilateral renal disease due to chronic nephritis A few casts were found in the urine

The value of the phthalein output over that of urea is strikingly demonstrated in the case just cited, elimination being practically equal for the two sides, but no indication was afforded of the reduced total renal function

In two out of three cases with hypernephroma a decrease in function was indicated In the third case no difference in function for the two sides was indicated The phthalein, the urea, specific gravity and quantity of urine collected from each side were identical and normal On account of pain due to a slight hydronephrosis, the kidney was explored and the tumor discovered The hypernephroma had not invaded the kidney but was simply attached to its upper pole, in all likelihood not interfering at all with renal function

The test has been used by us simultaneously with cystoscopy, phloridzin, indigocarmin and the polyuria test of Albarran` No particular advantage was added by combining with one or all Indigocarmin and phenolsulphonephthalein can be combined as follows Following the appearance of phthalein after injection, 5 c c of 4 per cent indigocarmin suspension is injected into the gluteal muscles and the time of appearance in the acid urine noted While the amount of phthalein excreted can be estimated with a fair degree of accuracy in the presence of indigocarmin by rendering the urine alkaline and boiling on the other hand the amount of indigocarmin excreted can be estimated after acidifying with hydrochloric acid or sulphuric acid at the best only roughly, and occasionally not at all When the two tests are used simultaneously the whole test is complicated with the introduction of no advantages and some disadvantages

In the following case, with a painful kidney with old healed pyelonephritis, various functional tests were combined, urea, phloridzin, cryoscopy and polyuria

Left	Right
325 c c	80 c c
Specific gravity 1010	Specific gravity 1009
Urea 40 6 cg	Urea 8 cg
Phthalein appeared 7 min	Phthalein appeared 8 min
Excretion 25 per cent for 1 hr	Excretion 8 8 per cent

Phloridzin test, injected 5 mg Sugar appeared in 15 min Trace in 35 minutes, 1 95 gm in 1 hour

Cryoscopy, urine for first 20 minutes 44 c c Δ —0 09 22Δ—0 15

Polyuria test

Left	Right
44 c c	22 c c
120 c c	22 c c
158 c c	41 c c

Urine collected in 20-minute periods

INHIBITION OF FUNCTION AS THE RESULT OF URETERAL CATHETERIZATION

As pointed out by Kapsammer,[39] a change in function of the kidney sometimes results from the introduction of the ureteral catheters and may occasionally seriously interfere with the value of quantitative determinations of the renal function Following catheterization anuria is most frequent but sometimes polyuria occurs and even in the presence of polyuria inhibition of secreting function, urea, etc , may be present In our series a moderate grade of inhibition has been noted in six cases out of seventy This inhibitory influence of the catheters can be readily detected by determining the total function without the use of catheters which should always be done as a control In no instance in our series was the inhibition of such a grade as to interfere seriously with the value of the test This inhibition of function from ureter catheters has also been noted by Keyes, Jr , and A R Stevens [40] The most serious disturbance in our experience occurs shortly after the introduction of the catheters and it is wise to wait until the catheters are working freely and smoothly before giving the phthalein injection If this technic is followed, inhibition will probably not play an important rôle in the great majority of cases

RENAL FUNCTION BEFORE AND AFTER NEPHRECTOMY

This problem has been investigated from the experimental and from the clinical side The cats employed in the diuretic work (referred to above) were utilized also for the study of this problem During the course of active secretion one kidney was suddenly tied off, the quantitative secretion of urine and phthalein being subsequently studied and compared with the excretion prior to this nephrectomy, the conditions of the experiment of course being kept absolutely the same after the removal of the one kidney In the majority of instances a slight fall both in the quantity of urine and in the phthalein excretion occurred immediately after tying off the one kidney, occasionally the phthalein remained the same for one-quarter or one-half hour and then gradually fell, and in one instance the urinary flow was increased while the phthalein output remained practically the same

One case is of particular interest inasmuch as the removal of one kidney greatly reduced the urinary flow and at the same time reduced the phthalein output to one-fifth of its former level This finding was unique In this case, however, it was found that the remaining kidney was congenitally atrophic or infantile in character and weighed only 6 4 gm , while the kidney which had been removed weighed 26 4 gm This is a striking example of the value of the test in detecting the true functional capacity of a kidney

39 Kapsammer See original paper, Ref 2
40 Keyes Personal communication

TABLE 12—AUTOPSY

Name	Date	Clinical Diagnosis	Microscopical Findings
1—R, aged 39 77101	3/28/11	Acute endocarditis, mitral insufficiency dyspnea no edema at time of test, developed later acute nephritis	Alb +, few casts
2—L, aged 16 77513	3/28/11	Arteriosclerosis, aortic insufficiency, acute endocarditis, dyspnea, some edema of legs	
3—G, aged 71 75711	11/9/10	Arteriosclerosis, bronchopneumonia hypertrophic arthritis deformans, blood pressure 220 225	Trace alb and occas cast
4—T, aged 35 77268	3/21/11	Chronic osteomyelitis, developed a tuberculous pneumonia	Alb +, and casts
5—McC about 60	3/31/10	Hypertrophy prostate, small residual	28 c c of urine excreted in two hours
6—M A aged 33 75555	11/6/10	Syphilitic nephritis, edema	Alb ++, few casts, clear
	11/11/10	Uremic	Alb ++, casts
7—Mrs W aged 21 77712	11/9/10	Nausea and vomiting, high grade choked disk, severe anemia, definite uremia	Alb +, no casts
8—T I, aged 37	1/3/11	Bilateral calculous pyonephritis, uremia	Alb +, cloudy from pu
	1/7/11	Some improvement, not so much nausea	Alb +, cloudy from pu
	1/9/11	Improving	Alb +, cloudy from pu
	1/11/11	Again severely uremic	
9—L, aged 76 Surg No 25319	1/22/10	Hypertrophy prostate, large residual, myocarditis, some dyspnea	Alb + and casts, clear
	1/29/10	Condition seems better, has had retention catheter	Alb + and casts, cloudy
	2/4/10	Condition same	Urine pale, cloudy from pus
10—G, aged 55 Surg No 25174	12/22/09	Hypertrophy of prostate, large residual, some anemia, slight nausea and vomiting	Trace alb, slightly cloud from pus
	1/7/10	Retention catheter, condition same, up and about ward, urine output, 2 3 liters, urea, 25 30 gm	Urine more cloudy
	1/10/10	More nausea and vomiting, injec 30 mg	Cloudy
11—H T aged 20 76691	1/20/11	Acute pneumonia, died 1/27/11, of abscess and gangrene of lung	
12—G, aged 12 77459	3/28/11	Diabetes insipidus clinical diagnosis, no signs of nephritis	Negative
	3/31/11	Same condition	No alb or casts
13—D aged 44 77782	4/19/11	Arteriosclerosis, chr nephritis, myocarditis, pericarditis, edema, dyspnea, Von Graefe, blood-pressure 110	Alb ++, few casts
14—B, aged 29 76710	1/20/11	Chr nephritis, aortic and mitral insufficiency, general anasarca dyspnea, in bad condition but not uremic, blood pressure 190	Alb +++ and shower of casts
15—O, aged 63	1/20/11	Hypernephroma of right kidney	200 c c from right
16—T, aged 60	7/?/10	Complete retention, due to contraction of vesical neck, chr abscess space of Retzius, bad clinical condition, bad cystitis	Cloudy, pus, small amount alb
17—P, aged 77	12/10/10	Hypertrophy of prostate, pyuria	Pus and alb
	12/19/10	Some fever, drowsy	
18—W, aged 66 Surg No 26508	9/7/10	Hypertrophy of prostate, myocarditis	Alb +, pus
	9/17/10	Catheter drainage	Alb +, pus
	10/1/10	Catheter drainage	Alb +, pus
19—L, aged 57	10/7/10	Carcinoma of prostate, pyuria	Alb +
	10/17/10		
	10/21/10		
20—P L aged 69 26236	7/19/10	Hypertrophy of prostate, acute retention, good condition	Pyuria
21—R, aged 69 Surg No 25637	3/24/10	Hypertrophy of prostate, retrovesical abscess, septic temperature, fracture hip, bad shape	Pyuria
	3/31/10		
	4/12/10	Very sick, suprapubic drainage	
	4/23/10		

* Left kidney excreted 44 per cent in 1 hour and 10 minutes, right kidney trace

TABLE 12—AUTOPSY

Time of Appearance (min.)	Percentage of Drug: One Hour	Percentage of Drug: Two Hours	Remarks
		39 5	Died 4/10/11 Autopsy Arteriosclerosis, myocarditis, acute mitral and tricuspid endocarditis, acute and moderate chronic diffuse nephritis, acute nephritis of only a few days' duration
		43 5	Died 4/8/11, of cerebral embolus Autopsy 3533 Ulcerative aortic endocarditis, acute vegetative endocarditis left auricle, cardiac dilatation and hypertrophy, chronic passive congestion of viscera
		15 5	Autopsy 3461 Atrophy of right kidney from old thrombosis of renal artery, left kidney shows chronic diffuse nephritis, small, granular kidney
		32 2	Autopsy Moderate grade of chronic diffuse nephritis
24	33 0	68 0	Died of pneumonia ten days later, no operation Autopsy Well developed double polycystic kidneys
	2 9	6 2	Died 11/16/10, in coma Autopsy Severe amyloid nephritis
	0 0	Trace 0 0	Died 11/14/10 Autopsy Small granular kidneys, superimposed acute nephritis
	0 0	0 0 Trace 5 5 Faint trace	1/11/11, double nephrotomy, died in twenty-four hours, both kidneys filled with calculi, being mere thin-walled pus sacs
30	24 4	49 0	Prostatectomy 2/4/10, died twelve hours after operation, of heart failure, ether anesthesia
16	31 0	42 8	Autopsy Some myocarditis and arteriosclerosis, slight chronic nephritis, slight dilatation of pelves, discrete scattered areas of acute pyelonephritis
17	8 8	33 8	
40		Trace	Went into coma 1/18/10 and died 1/19/10
30		Trace	Autopsy Some dilatation of pelves, which were filled with pus, marked grades of interstitial nephritis, kidneys being ⅓ normal size, some diffuse pyelonephritis
23		Trace 57 0	Autopsy 3499 Fatty degeneration of viscera, including kidneys
		6 0	Died in uremia 4/9/11
		3 0	Autopsy Extreme grade of chronic interstitial nephritis,, cortex almost destroyed, superimposed acute nephritis (?)
		16 1	Died from heart condition, 4/20/11 Autopsy Myocarditis, pericarditis, kidneys show arteriosclerotic scars with a mild chronic diffuse nephritis and a marked chronic glomular nephritis
		26 6	Died 1/21/11 Autopsy 3494 Chronic and acute mitral and aortic myocarditis, marked cardiac dilatation, acute and moderate chronic diffuse nephritis
8	*		Nephrectomy and right kidney found almost entirely destroyed, died four days later, of hemorrhage, autopsy showed a large hypertrophied kidney with microscopically some very slight chronic nephritis
30	6 0	16 0	Died two weeks after test Autopsy Dilatation of both renal pelves and marked grade of chronic bilateral pyelonephritis
8	18 5	43 5	Died ten days after last test, in uremia
23	8 0	13 0	Autopsy 3488 Old chronic pyonephrosis of left kidney, right kidney hypertrophied but showing chronic diffuse nephritis and a marked diffuse acute pyelonephritis
15	16 0	31 2	Prostatectomy successful, two weeks after operation myocarditis became aggravated, uremia developed, ending in death
	25 0	38 0	
	18 0	30 5	Autopsy 3474 Infantile right kidney, left kidney showed chronic diffuse nephritis
25	Trace	7 1	Prostatectomy under gas anesthesia, did well for ten days, became constipated, uremia developed and died some days later
40	7 0	12 5	Autopsy 3466 Acute ureteritis and pyelitis, chronic diffuse nephritis of severe grade
25	5 0	12 0	Died on third day following prostatectomy, from cerebral hemorrhage Autopsy Kidneys show an arteriosclerotic form of nephritis
15	15 1	29 3	Died 4/25/10 Autopsy Chronic myocarditis, arteriosclerosis, chronic cystitis, hypertrophy of prostate, retrovesical abscess, kidneys showed some chronic diffuse nephritis with marked epithelial necrosis, the latter being, of course, a terminal occurrence
14	13 8	33 8	
13	25 5	58 0	
30	15 0	40 0	
13	16 6	45 2	

The function of the two kidneys on the day of the operation has been estimated and compared with the function of the remaining kidney as it is on the day following operation Chart 14 shows the curve of excretion prior to and the day following nephrectomy in a dog, the estimations being made at five-minute intervals after the appearance of the drug in the urine following an intravenous injection of 6 mg of phthalein Although the rate of excretion is somewhat slower, no great decrease in function is indicated at the end of a half-hour's observation

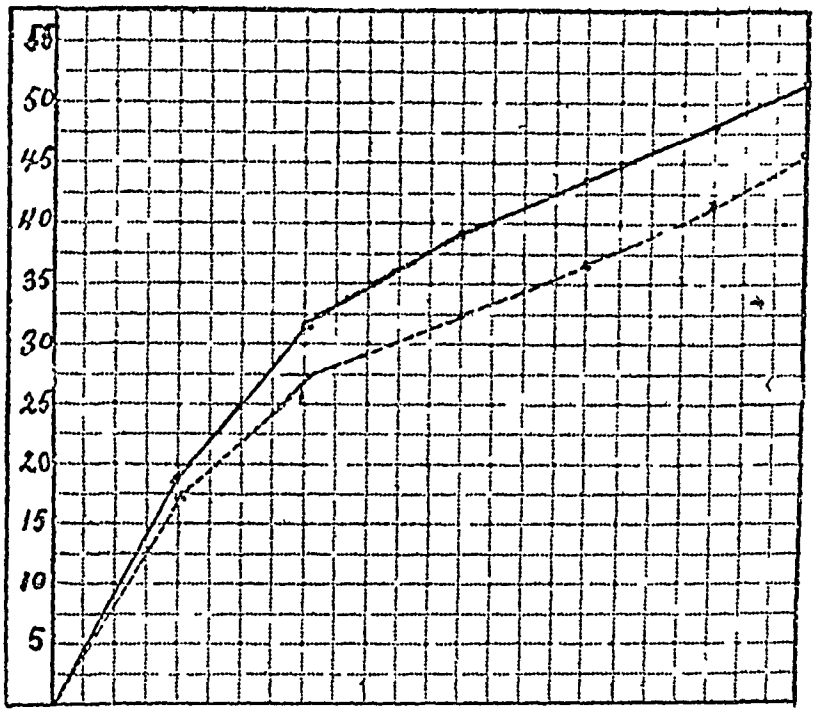

Chart 14 —The upper line represents the phthalein excretion for one half hour following intravenous injection, the estimations being made at five minute intervals The lower line represents the excretion in the same dog for one kidney within twenty-four hours after nephrectomy

In those cases in which the function of the remaining healthy kidney was estimated after an interval of three weeks to one month following nephrectomy, the function was invariably found not merely to equal the combined function of the diseased and healthy kidney prior to operation, but to be definitely greater In a few cases in which the function was estimated at an interval of a few days to a week following nephrectomy, the function corresponds very closely to that which existed in that kidney previous to operation, but at the end of a period of three weeks or a month the function was always equal to that of two normal kidneys

In one case of double renal tuberculosis in which the function of the kidney left behind was 26 per cent for one hour prior to operation, it increased until at the end of one month a phthalein excretion of 50 per cent for one hour was attained, which was considerably greater than the combined function of the two kidneys prior to operation In this instance

the tuberculous focus was probably small and confined, so that the remaining healthy portion probably underwent compensatory hypertrophy

COMPARISON OF PHTHALEIN EXCRETION WITH AUTOPSY FINDINGS

An opportunity was afforded in twenty-one cases (see Table 12) of comparing the phthalein excretion with the pathological condition of the kidneys at autopsy

In the cases in which the phthalein excretion was moderately decreased the kidneys showed moderate pathological changes In those cases in which no phthalein was excreted, or only a small amount, extensive and severe renal destruction was invariably found

In one heart case (No 14, Table 12) showing an excretion of 43 5 per cent for two hours, which is a definite but moderate reduction, only a passive congestion was found That this condition can interfere with function other clinical cases seem to confirm

In one case double polycystic kidneys were encountered, although the phthalein excretion was normal The patient exhibited no symptoms from this condition during life, death being due to pneumonia The fact that polycystic kidneys may be present for a great many years without symptoms and also that they are usually unexpectedly discovered at autopsy in patients dying from other conditions is good proof of their functional efficiency

CONCLUSIONS

1 The absorption of phenolsulphonephthalein following injection into the lumbar muscles is better than the absorption from the gluteal injection, while the latter is superior to subcutaneous injection

2 Administration into the lumbar muscles is the method of choice

3 Experimentally those diuretics that stimulate the renal cells to increased activity cause some increased secretion of phenolsulphonephthalein, while those that act mechanically produce no increased secretion Clinically diuretics do not influence the phthalein output

4 Experimental evidence seems to indicate that phenolsulphonephthalein is excreted mostly by the tubules but probably also to a slight extent by the glomeruli

5 The renal cells display a striking specificity in the excretion of phenolsulphonephthalein

6 The phenolsulphonephthalein as used by us has many advantages over all other functional tests so far proposed

7 It is better adapted for use as a functional test than any other drug previously employed for the same purpose, on account of its early appearance in the urine and the rapidity and completeness of its elimination by the kidney and the reliance to be placed on its findings

8 The method of quantitative estimation of the amount of drug excreted is simple and exceedingly accurate

9 It is of immense value from a diagnostic and prognostic standpoint in nephritis inasmuch as it reveals the degree of functional derangement in nephritis whether of the acute or chronic variety

10 In the cardiorenal cases so far studied the test has proved of value in determining to what degree renal insufficiency was responsible for the clinical picture presented

11 The test has proved of value not only in diagnosing uremia from conditions simulating it, but has also successfully indicated that uremia was impending when no clinical evidence of its existence at the time was present

12 The test has proved of great value in revealing the true renal condition in cases of urinary obstruction It is here of more value than the urinary output, total solids, urea or total nitrogen, and enables the surgeon to select a time for operation when the kidneys are in their most favorable functional condition The improvement in the renal condition in cases of urinary obstruction following the institution of preliminary treatment is strikingly indicated by this test

13 In unilateral and bilateral kidney diseases the absolute amount of work done by each kidney as well as the relative proportion can be determined when the urines are obtained separately

It is with the greatest pleasure that we thank Dr H H Young for his early and continued interest in this work and for the generous supply of clinical material referred to us by him, Dr Barker, Dr Thayer and the other members of the staff of the medical clinic for the opportunity of studying the cardiac and nephritic cases, Dr G L Hunner and Dr E K Cullen for the privilege of studying many surgical affections of the kidney, Dr F W Hobleman for his valuable assistance in carrying on the work, and Dr Dunning of the firm of Hynson and Wescott for the sulphonephthalein employed throughout this investigation

A CASE OF PANCREATIC DIABETES MELLITUS *

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Patients presenting glycosuria coupled with deficient fat and protein absorption are among the rarities of a wide medical experience These, however, are the cases of diabetes mellitus that make the clinician and physiologist certain in their belief that the pancreatic gland is intimately connected with the metabolism of carbohydrates, and that the other forms of the disease, although not yielding such clear-cut signs, may have a similar origin

The following report of such a case is thought to be of value, especially as it was found that the treatment of this patient by means of pancreatic gland yielded results which proved to be of great interest

I am indebted to Dr T C Janeway, under whose supervision the patient was treated, for the following data

CASE REPORT

History (May 9, 1910) —The patient is a college student, aged 20 His maternal grandmother died of tuberculosis, his mother suffers from a cardiac trouble, his father recovered from an attack of Bright's disease twenty years ago There is no history of diabetes, obesity or other hereditary disease One brother and one sister are alive and well Excepting mild attacks of measles and mumps in early childhood there has been no illness The patient's habits are exemplary, he scarcely ever drinks or smokes, has not been the subject of any venereal disease, is not prone to worry excessively about examinations, etc, and his appetite has been hearty but not abnormal for a young man of his age

In February, 1909, he was thrown to the floor while playing basket ball and struck the back of his head During the following evening and night he was confused and irrational, but on the next day all symptoms had disappeared There was no headache, no polyuria, no thirst and no indication whatever of cerebral injury or glycosuria The urine was not examined

In the latter part of November, 1909, he had an attack of intense abdominal pain without diarrhea or fever Early in December, while preparing for examinations and training for the 100 and 220 yards dash in some indoor games, he realized that he became tired easily Toward the end of December this lassitude led him to consult a physician The urine contained sugar, reported at 8 per cent In January, 1910, he was subject to frequent attacks of vomiting accompanied by a "burning sensation," but no frank abdominal pain In February the vomiting ceased, the stools, however, at this time changed in character, became large and putty-like, and were said to resemble "mayonnaise" The feces have continued to be of a similar nature most of the time up to the present The patient's original weight was 138 pounds The maximum quantity of urine collected during a twenty-four-hour period was between 5 and 6 quarts The maximum amount of

*From the service of Dr T C Janeway, St Luke's Hospital, and from the Laboratory of Biological Chemistry, Columbia University, College of Physicians and Surgeons, New York City

sugar observed has been 8 per cent No treatment nor diet had been instituted at any time

Physical Examination (May 9, 1910) —The patient weighs 113 pounds, is 5 feet 9 inches in height The general condition is that of extreme emaciation, all the ribs stand out prominently, the cheeks are hollow Weakness and languor are expressed in every movement The skin and mucous membranes are pale The tongue is dry, white and glazed The thyroid gland appears to be of normal size The pulse rate is 52 The systolic blood pressure while the patient is in the recumbent position is 90 The radial arteries are very soft and small The heart and lungs yield no abnormal signs The respiration is of normal type The abdomen is moderately distended, most markedly in its lower half The lateral veins are somewhat prominent There are no signs of ascites The liver and spleen are not palpable, nor do they appear enlarged on percussion The superficial lymph nodes are not enlarged The knee jerks are normal There is slight edema of the lower legs and feet Blood examination shows hemoglobin 75 to 80 per cent The stools resemble the description of them given by the patient in the history They are very voluminous, formed, though soft, and number 1 to 4 a day, their odor is foul, their color greenish yellow On microscopic examination they show many undigested muscle fibers much free fat and many fatty acid crystals Dr Hopkins of the St Luke's Hospital Pathological Staff finds the reaction for trypsin negative

The appended table gives the essential results of the quantitative urinary examinations, the diet employed and the treatment administered The total nitrogen was determined by the Kjeldahl process, the ammonia by the Folin[1] method beta-oxybutyric acid and its derivatives by Shaffer's[2] method, and the sugar by polariscopic reading before and after fermentation

TABLE GIVING QUANTITATIVE URINARY RESULTS, COMPOSITION OF DIET AND MEDICATION

Date, 1910	In Urine in Twenty-Four Hours: Glucose, gm	Total N, gm	Ammonia, gm	Ammonia N as Per Cent of Total N	Acetone and Diacetic Acid, gm	Beta-Oxybutyric Acid, gm	Total Acid Substances as Beta-Oxybutyric Acid, gm	Diet: Fat, gm	Carbohydrate, gm	Protein, gm	Number of Stools Per Day	Remarks ‡
May 11	137 5	17 5	2 8	13 3	1 7	2 4	5 3	225	65	135	3	"Pankreon" 0 5 gm three times a day, May 11-19
May 12	88 0		0 3					225	60	135	1	
May 13	94 7	20 7	1 9	7 7	1 6	1 9	4 9	225	60	135	4	
May 16	95 2		1 6					225	45	130	2	
May 19§	94 0	27 7	2 9	8 3				220	0	245	4	
May 24	45 5	11 8	0 9	6 0				125	0	165	1	Raw sheep's pancreas 50 gm three times a day, May 20 29
May 26	91 3	26 5	5 2	16 3	6 4	17 9	29 3	125	0	165	1	
May 27	68 5	22 4	6 0	22 0	5 2	25 4	34 8	80*	5	40	1	
May 28	86 5		5 3					220	15	125	0	
May 30	80 0		5 0					275†	170	100	1	

* "Green" day
† "Oatmeal" day
‡ Sodium bicarbonate, 30 gm, was given on each day except May 30
§ Thymus gland was administered on May 19, as the butcher had furnished the wrong material, on the next and following days pancreatic gland was given

There is no possible doubt that this patient is suffering from diabetes mellitus of a severe type The constancy of the glycosuria when the

1 Folin, O Am Jour Physiol, 1905, xiii, 45
2 Shaffer, P Jour Biol Chem, 1908, v, 211

amount of carbohydrate in the food was diminished and the presence of moderate amounts of beta-oxybutyric acid, tested for on May 11 and 13, establish this diagnosis As in all cases of diabetes mellitus, a more difficult problem is encountered when it becomes necessary to identify the cause of the disease In this instance two possibilities present themselves (1) the traumatic cerebral injury contracted in February, 1909, (2) a lesion of the pancreas

1 The causal relation between cerebral trauma and diabetes has been appreciated for many years [3] Usually such an injury is one which affects the skull directly and is followed by symptoms of cerebral concussion Both of these conditions apply to the present case Further data are needed, however, to establish this etiological relationship In the absence of adequate urinary examinations immediately before and after the accident, the necessary criteria, according to Von Noorden,[4] are loss of weight and strength within a few weeks of the accident, neuralgias disturbances of vision, increased thirst, cramps in the calves of the legs, sexual impotence, or other symptoms of diabetes and a glycosuria If these symptoms develop within one or two years of the accident, even though the intervening period was free from any diabetic manifestations, the cerebral condition must be admitted as a possible factor in the disease In the case under discussion the trauma was followed by well-marked signs of concussion of the brain and within ten months there were evidences of the beginning of diabetes While the possibility of an etiological connection must therefore be conceded, it is not probable in this case Cerebral trauma and concussion are of frequent occurrence especially among those engaged in athletics, while a sequel of diabetes mellitus is very rarely found Furthermore, there is here definite evidence of pancreatic involvement which in itself would be sufficient to account for the disease

2 The large volume of the stools, their fatty character and great content of undigested muscle fiber, coupled with the absence of trypsin, point to a lesion of the pancreas resulting in deficient secretion into the intestine The glycosuria and acidosis indicate a lack of the internal secretion It may therefore be concluded that the function of the gland has been almost entirely, if not completely, lost A pancreatic calculus would account for the attack of abdominal pain in November, 1909 and a closure of the duct of the gland, followed by sclerosis, for the remaining symptoms

Of the various forms of pancreatic disease, calculus was the first to be recognized as a cause of diabetes mellitus [5] In similar cases C von

3 Naunyn, B Der Diabetes mellitus, Vienna, 1906, p 77

4 Von Noorden, C Die Zuckerkrankheit und ihre Behandlung, Berlin, 1910, p 68

5 Naunyn, B Der Diabetes mellitus, p 122

Noorden[6] gives the choice of diagnosis as one of two either a tumor or a calculus closing the duct of Wirsung In the present instance the diagnosis of malignant growth was not considered probable and the subsequent course of events, as will be detailed below, confirmed this opinion Falta,[7] while mentioning various other pancreatic diseases, claims that the most frequent cause of the syndrome under discussion is pancreatic lithiasis This was regarded as the diagnosis in the present case and therapeutic effort was concentrated on it

There are two forms of pancreatic medication

1 The Preparations of Extract of Pancreas—Various brands have been put on the market "Pankreon" is perhaps the one most favorably regarded It consists of pancreatic extract hardened with tannin to resist the destructive action of the acid gastric juice and allow the ingredients of the extract to pass into the intestine in an active condition Many reports[8] (the reference list is not complete) of the use of this and similar preparations have been made Among many successful trials of such extracts numerous failures are recorded Extracts of pancreas have been given intravenously[9] The diabetic glycosuria has been reduced thereby but the secondary effects of the injection, rise of temperature, marked prostration, etc, have been so severe as to make this method of administration of doubtful value

2 The Raw Pancreatic Gland of the Sheep and Other Animals—The raw gland administered by mouth has proved to be far more reliable than the extracts

In the present case, "Pankreon" given in 0 5 gm doses three times a day resulted in no change, while the administration of sheep's pancreatic gland taken raw and prepared as salad in 50 gm portions three times a day, brought about a very marked improvement The stools changed from those typical of pancreatic disease to what appeared to be normal movements

The indications of increased fat absorption and its clinical significance in this instance are of the greatest interest and importance Ordinarily fat digestion would be signalized by no changes in urinary secretion which could be appealed to as tests In advanced cases of diabetes mellitus, however, beta-oxybutyric acid, diacetic acid and acetone are found in the urine These substances, as we now know from the work of many

6 Von Noorden, C Die Zuckerkrankheit, p 179

7 Falta, W Ergebn d inn Med u Kinderh, 1908, II, 74

8 Falta, W Ergebn d inn Med u Kinderh, 1908, II, 79, Von Noorden, C Die Zuckerkrankheit, p 184, Pratt, J Am Soc Advanc Clin Investig, Sec An Mt, May 2, 1910, p 6, Gigon, A Ztschr f klin Med, 1907, lxiii, 420, Salomon, H Berl klin Wchnschr, 1902, xxxix, 45

9 Zuelzer, G Ztschr f exper Path u Therap, 1908, v, 307 Zuelzer, G, Dohrn, M, and Marxer, A Deutsch med Wchnschr, 1908, xxxiv, 1380 Forschbach, J Deutsch med Wchnschr, 1909, xxxv, 2053

observers,[10] are derived principally from fatty acids and to a much less extent from amino-acids An assimilation of fat would therefore be expected to cause an increase in the acidosis The increased formation of these acid substances would necessitate their combination with the available alkali, and would result in a marked advance in the urinary ammonia values Both of these facts are conclusively demonstrated in the accompanying analyses The daily output of ammonia averaged 1 7 gm and that of total acid derivatives as beta-oxybutyric acid 2 2 gm before sheep's pancreas was given During the succeeding days, when the raw gland was administered, the ammonia excretion rose to an average of 5 4 gm and the acid substances to 32 1 gm These very substantial increases cannot be attributed to any change in medication, as might have been the case if the amounts of bicarbonate of soda (see table) had been varied, nor were the differences in the diet great enough to account for them

As far as it is possible to ascertain from the literature, this fact has been observed only once before Salomon[8] demonstrated increased amounts of acetone in the urine after the use of "Pankreon" in a case of pancreatic diabetes, the diacetic and beta-oxybutyric acids were not determined Furthermore, the absence of excretion of beta-oxybutyric acid in dogs suffering from diabetes after pancreatic extirpation may be explained on similar grounds, that is, non-absorption of fat, while in cases of phloridzin diabetes in dogs, where fat absorption is normal, acid substances appear in the urine, at least at a time when the nitrogen balance is negative

Brugsch and Bamberg,[11] puzzling over the difference between these two forms of experimental diabetes, advanced various inconclusive hypotheses The present explanation, however, of deficient fat absorption and consequent lack of fatty acids from which to develop the acid substances, is a simple one, and is substantiated not only by the negative findings in cases of extirpated pancreas in dogs, but also by the appearance, in the case here reported, of an increase in the urinary acid substances after the administration of raw pancreatic gland To produce an increased absorption of protein and fat is the keynote of successful treatment of pancreatic diabetes, since the only other important food element, namely, the carbohydrate, is rendered valueless to the body on account of its excretion as unoxidized glucose in the urine Without pancreatic medication, death from starvation would result in a case of this kind, in spite of an abundant food-supply

10 Magnus-Levy Ergebn d inn Med u Kinderh, 1908 1, 352 (A summary of the entire subject of acidosis is given in this paper)

11 Brugsch, T, and Bamberg, K Zentralbl f Stoffwechselkrankh, 1908, iii, 1, Baer, J Arch f exper Path u Pharmakol, 1904, li, 271

When the absorption of fats and proteins brings about a high degree of acidosis, as indicated by the great increase in beta-oxybutyric acid excretion, there is the obvious danger of acid intoxication and diabetic coma In the present case danger signals appeared when the pancreatic gland was used For a time the symptoms became so threatening that the medication was stopped and a bad prognosis seemed justified

The influence of the bicarbonate of soda is well shown in the ammonia output On May 11, the first day of its administration, the ammonia output was higher than on the succeeding days when the ratio of ammonia nitrogen to the total nitrogen was also lower, both figures being again increased as the excretion of acid substances became greater A second effect of this drug, frequently noted in diabetes, was also observed Toward the end of the patient's stay at the hospital, edema of the face and extremities had developed to such an extent as to make discontinuance of the bicarbonate of soda necessary

Subsequently, through June, July, August, September and October, the use of the pancreatic gland was resumed and at the same time measured amounts of carbohydrate were allowed [12] The patient gained strength on this régime and has been able to enjoy an outdoor life of moderate activity The amounts of excreted ammonia remained high but were less than during the first pancreatic gland period in May These observations may be explained on the supposition that the original period of acid intoxication, with what appeared to be impending coma was due to the sudden flooding of the system by acid substances with which the tissues were not prepared to deal whereas at a later time the body adapted itself to these poisons to a certain extent An acid excretion of equal intensity occurs not infrequently in cases of diabetes mellitus without calling forth any symptoms of distress Such patients, however, have to meet a gradually increasing acidosis and not a sudden one, and may therefore be able to regulate their metabolism accordingly

Another factor that may have been of aid in this case was the allowance of carbohydrates when the danger from acid auto-intoxication was recognized Carbohydrates, in diabetics are never completely excreted in the urine but, as has been recognized in calorimetric determinations are always oxidized to some extent and therefore diminish the output of acetone and its precursors Tolerance of the poisons, an allowance of carbohydrates, together with the use of bicarbonate of soda, made it possible for this patient to continue the use of pancreatic tissue, regain considerable strength and enjoy a comfortable existence for some time

One further point remains for consideration, and this is one of the most disappointing chapters in medicine How does the administration

12 For data subsequent to May 30, 1910, I am indebted to Dr Thomas B Carpenter of Buffalo

of pancreatic tissue affect the glycosuria? In other words, can the internal secretion of the gland be replaced? In the ordinary types of diabetes this cannot be done, but is the condition not somewhat different in the pancreatic variety of the disease? Most observers believe that, no matter what the etiology of the diabetes, there is no difference in this regard However, Wegele[13] claims to have attained the disappearance of the glycosuria with the use of "Pankreon" In dogs suffering from pancreatic diabetes, Piatt[8] was able to raise the limit of sugar assimilation after prolonged administration of raw pancreatic tissue In the present case, after four months' use of the gland, the carbohydrate balance appears little changed The nutrition, however, has not retrogressed

If any conclusions are justified after the treatment of but one case and the review of the reports that have gone before, the following may be tentatively advanced In pancreatic cases of diabetes mellitus associated with deficient digestion of proteins and fats, extracts of pancreas such as "Pankreon" *may* be of service but more certain results are obtained with raw pancreatic gland The better absorption of food that follows the pancreatic medication brings about improved nutrition on the one hand and the dangers of a marked acidosis on the other The latter must be carefully guarded against by including sufficient carbohydrate and a minimum of fat in the diet, and by the use of bicarbonate of soda The glycosuria of any form of diabetes is not influenced by the administration of the pancreatic gland by mouth for a limited period Whether its more prolonged use will prove partially successful in this respect, as in the dog experiments alluded to above, is a matter for future trial

157 West Seventy-Ninth Street

13 Wegele, C Fortschr d Med, 1902, xx, 313

ORTHODIASCOPIC OBSERVATIONS CONCERNING A CERTAIN TYPE OF SMALL HEART AND ITS RELATIONS TO SOME GENERAL SYSTEMIC AFFECTIONS

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NEW YORK

The founder of modern medicine Laennec, who was the first to elaborate methods of auscultation and percussion and to found thereon an almost complete system of clinical medicine, had already made a profound study of the relative size of the heart under varying pathological conditions In later times the work of Virchow, of Beneke and the laborious and admirably accurate work of Wilhelm Muller contributed largely to our knowledge of the subject It is needless to dwell on the wonderful achievements of the more modern work, both physiological and anatomical, of Engelmann, His, Aschoff Tawara, Keith Albrecht and numerous others But all these studies and experiments were done either on the hearts of animals or on the human heart after death Then came the time when the Roentgen rays were applied to internal medicine and by these means the observer was enabled for the first time to study the living human heart *while in action,* and by means of a large screen the opportunity was given to study the heart in its varying size and position and in its relation to the other organs of the chest and upper abdomen The orthodiascope in particular enabled the observer to study the silhouette of the heart and large vessels as they are projected on the screen by means of parallel rays The most recent developments in the methods of studying the heart, the simultaneous tracings of venous, arterial and heart pulsations, and that most delicate of instruments, the electrocardiograph, have somewhat overshadowed the use of the orthodiascope, which latter, only a few years ago, caused great enthusiasm While welcoming the latest methods and their results, it would be foolish to regard the orthodiascope as antiquated and useless Each method of observation has its own peculiar value as an instrument of research, as well as its individual limitations, and we should greet with pleasure a multiplicity of methods confident that each new one that may arise will assist in the ultimate solution of these vital but most complex problems The orthodiascope, or, failing that, the simple Roentgen apparatus, is easy enough in its management to be used not only in the hospital or clinic but also in the private office, and any practitioner can easily become familiar with the necessary manipulations

A few words concerning the method employed in taking the heart tracings on which this study is based It must be remembered that the heart itself is not seen, but only its shadow, as well as the shadow of the large vessels and the other thoracic viscera This silhouette of the heart and large vessels is naturally subject to distortions, minimized, it is true, by the parallelism of the orthodiagraphic rays, but still sufficiently troublesome and attributable to manifold causes Great caution, therefore, and long experience are required to enable one to interpret correctly the foreshortenings and the various changes in form which the heart shadow presents Numerous pathological conditions of the lungs and pleuræ, abnormal contents of the thoracic cavity or the mediastinum, instability of position and shape of the diaphragm, may contribute to variations in the heart silhouette Nevertheless, with increasing experience and practice and with careful comparative study on the cadaver, it is found that certain configurations of the heart shadow correspond approximately to the normal and that there are others that undoubtedly represent pathological deformities In recognition of this fact, enthusiastic workers in this field, as Moritz, Dietlen, De la Camp, and Groedel, have elaborated systems of measurements by means of which the size and configuration of the normal heart shadow is to be determined for both sexes and for every period of life It has been found that certain very serious and unavoidable limitations detract from the usefulness and scientific precision of these measurements It is obvious that the lower part of the heart can scarcely ever be made so plainly visible by the orthodiascope as to be traced with any degree of accuracy This of course, is due to the interference of the diaphragm behind which the lower portion of the heart is apt to be hidden The longitudinal diameter, too, depending as it does on the recognition of the boundary between the large veins and the right auricle, is extremely difficult to locate and is a quantity, in the determination of which the personal equation plays a great and rather uncomfortable rôle In our own work the personal equation has to a great extent been eliminated by the fact that all tracings of the heart shadow and the large vessels were always and without exception done by one of us (Dr Krehbiel) Nevertheless, we have practically thrown out of our calculations the so-called longitudinal diameter and have, in measuring the hearts, relied almost entirely on the transverse diameter (which can always be determined with sufficient exactness), the varying inclination of the heart shadow with reference to the median line, and the general aspect and behavior of the heart under changing conditions Our method, then, briefly stated, is as follows The patient stands upright on a little platform against a vertical board made of basswood There are wooden flanges on both sides of this board which, if occasion requires, are easily adjusted so as to prevent the patient from

swaying to either side We have chosen the vertical position as the most convenient and our measurements therefore, are not comparable to measurements taken when the patient is in a horizontal position We use the old De la Camp model of orthodiascope, not only because we think it simpler and more readily handled, but also because it admits of the use of a very large fluorescent screen not for tracing but for the general survey of the chest and its organs Our screen is 12 by 16 inches, and by means of this we study in every case the position of the heart its relation to the lungs and other thoracic viscera, as well as to the diaphragm and the liver and stomach, which are all viewed simultaneously We consider this point of great importance and apt to prevent many errors, while many interesting and valuable facts can be obtained only by these means The survey of the chest and abdomen completed the tracing-screen is put on and a rapid tracing of the heart is made As a rule the lungs are not included in the sketch because, in our opinion, they tend rather to obscure the outline of the heart shadow The necessary fixed points in the tracing are the jugular notch of the sternum the clavicles, the nipples and the diaphragm The tracing of the heart is done by the usual dotting method, taking care to place the dots in the pause between inspiration and expiration We prefer this method to photographing the heart shadow and all that pertains to it because, in our opinion, sharper and more easily measured outlines result Nevertheless, we have in many cases taken photographic plates to compare with our tracings We wish to add that we have considered as entirely useless the estimation of the total area of the heart shadow, as traced by the orthodiascope, and have therefore not regarded it in our work Our reasons will be appreciated when it is remembered that we are not able to delimit with any certainty the lower part of the heart and to determine with any certitude where the heart ends and the aorta begins, hence it is quite evident that any calculation of the surface area of the heart shadow is more or less illusory

The necessity is obvious of having some standard with which the measurements are to be compared, whether or not that standard be exact We have selected the tables given by Groedel, mainly because they are based on tracings in the upright position, and we have considered as small any heart which falls below the minimum measurements assumed by Groedel as normal for the corresponding size and sex In many of the tracings which we consider as belonging to this type of microcardia, all the measurements were below the normal, in others, only the transverse diameter was below normal In order to avoid any error, as for example that of putting down a heart as small which may have appeared small only momentarily on account of some temporary variation in the position of the diaphragm, or some disturbance in the other thoracic

viscera, we have taken the tracings repeatedly in the same person at different times separated by sufficient intervals, and we have accepted none as abnormal that did not give the same measurements whenever the tracing was made

By this method of studying the living human heart we have very frequently encountered a certain type of small heart which, so far as our present experience goes, seems always to be accompanied by a certain set of clinical symptoms The syndrome occurs in males as well as in females, although it appears that females are more predisposed The time of observation, however, has been comparatively so short that we are not able to give actual figures in proof of this assertion As a rule, there are no subjective symptoms on the part of the heart Very rarely there was a complaint of slight palpitation or some shortness of breath on moderate exertion The symptoms most often complained of are due to irregularities of the nervous system, either of the peripheral nervous system, or else of the psychic sphere, or of both Usually the patients belonging to this class complain of stomach trouble A close study of the history will nearly always disclose the fact that they have suffered more or less gastric distress as long as they can remember They show all those disturbances which are commonly attributed to hyperacidity and the formation of gas, and which so frequently pass under the name of gastritis, intestinal fermentation, etc Examination of the stomach contents after a test-meal commonly shows a greater or less degree of hyperacidity, or rather of hyperchlorhydria, but no signs of ulceration or of any other organic lesion — simply the purely nervous form of excessive acidity So, too, careful and repeated examination of the feces shows nothing abnormal, notwithstanding the continuous complaint of gas formation and distress from distention of the intestines Patients of this class are thus frequently found in the hands of stomach specialists, where stomach washings, intestinal irrigations, medications and diets of all sorts are experimented on for years with but very little result Then, after having been told sufficiently often that they are nervous, the nerve specialist gets his chance, and electricity, massage, hydrotherapy, suggestion, and even Christian Science are attempted — but in vain

Besides these peripheral symptoms, there are very distinct and constant psychic signs It can be asserted with great positiveness that the patients under consideration are in no way hysterical They are not "putting on", they are not playing sick in order to be the center of attention or to dominate their surroundings Their complaints do not alter, but remain stationary, and the patients are most anxious to get well In all the cases which we have considered as typical, not a sign or symptom of hysteria has been detected The characteristic symptoms associated with the peculiar type of small heart to which we wish to

draw attention are of an entirely different class These patients are usually very much depressed and are very frequently subject to attacks of profound hypochondria, of longer or shorter duration The symptoms thus far mentioned, it is needless to say occur very often *not* accompanied with the small heart, but in that event not only is the hysterical status very frequently distinctly present, but the syndrome which we have just briefly described is distinguished from other forms of hyperacidity and hypochondriasis by the fact that our form of disease, which we may for the present and for want of a better term call "microcardia" is *congenital,* while all the other forms presenting similar clinical symptoms are acquired (severe shock strong emotional influences, or numerous other causal factors)

The small heart which we consider characteristic of this form of microcardia differs very markedly from other forms of small heart For instance, it is not at all like the heart of the tuberculous the so-called "drop-heart" (*Tropfenherz*) of the Germans, nor does it resemble the heart of the narrow-chested, as described by Krauss in his brilliant article Hearts very similar to the kind of heart under discussion have been called the "heart of the weakling' Still this does not entirely cover the ground, since very often patients afflicted with microcardia cannot at all be put into the class of the weaklings The heart that we mean is simply small It may be small in all directions — usually it is below the normal minimum in the transverse axis Virchow, it will be remembered, mentions the narrow aorta, and just in passing, a possibly small heart of the chlorotic The cases we refer to are not necessarily chlorotic, on the contrary, they very frequently have a fully normal blood-count and the aorta is very often of normal width and apparently of normal length and not at all the "aorta angusta' of Virchow although that form may also occur The heart is fully developed, and in most cases the left ventricle and auricle especially come forward in the heart shadow with all desirable distinctness The inclination of the heart toward the vertical is usually quite normal, only in rare cases being somewhat more obtuse than under normal conditions The blood-pressure is, as a rule, slightly below the normal, although we have seen quite a number of cases with normal blood-pressure The examination of the blood occasionally shows a certain degree of anemia, but very frequently conditions are entirely normal

We have begun to test the muscular vigor of these small hearts by the aid of the ergograph, but have not as yet a sufficiently large number of tests to give positive figures We can only say, in a general way, that these small hearts are somewhat more easily fatigued and cause slight dyspnea more easily than normal hearts There is, however, not the

slightest trace of deficiency in the heart-muscle itself The heart is simply congenitally small

We have not been able to examine the hearts of very small children because we could not get them to keep still, but we have examples of children of 14, even of 11 years, a time when the development of the heart should be proportionately great, in which the heart was, on the contrary, small, but, as above stated, there was not the slightest sign of deficiency of muscle We may also add that we have never found in the true and uncomplicated cases any signs of myocarditis We have had occasion to observe one or two of these small heart cases for quite a number of years, from youth until later middle age, but have not found the slightest change in the muscular condition of the heart, nor have we found any of the usual secondary symptoms of cardiac insufficiency or myodegeneration — no enlargement of liver or spleen and no nephritis, or edema, etc

We wish to quote here a passage from Laennec's treatise on "L'Auscultation Mediate," [1] this quotation showing the wonderful genius of Laennec and his almost incredible clinical and pathological insight

> I do not think that diminution of the size of the heart can in any case be considered a disease I have never observed any symptom which could be attributed to this cause, or rather, those persons in whom it was found all appeared to me less subject than usual to inflammatory affections and disorders of the circulation I may remark, however, that several hypochondriacs, who were liable to faintings from various slight causes, gave, under the stethoscope, signs of a very small heart, and we know, moreover, that women, who are much more liable to these attacks than men, have in general smaller hearts

The tracings, drawn with the orthodiascope, illustrate what has been said above As will be seen, we give all the measurements usual in orthodiascopic study of the heart, including the total area

In order that the difference between the normal heart and the abnormally small one may be seen and the different cases compared with measurements made by others, we have reproduced, in Figure 1 the heart of an adult male, which in every essential respect, as far as can be seen, is perfectly normal Figure 2 shows the heart of an adult female which is also, according to all means of diagnosis, perfectly normal In this figure the orthodiascopic picture of the lungs is filled out, merely to show that it is better, for studying the figure of the heart, to draw the heart and aorta alone It may be of interest to know that Figure 2 is, in addition, a good instance of what has been said about microcardia and its accompanying symptoms as being congenital The woman whose heart is here represented has for nine years been subject to all of the symptoms men-

1 Laennec L'Auscultation médiate, transl by Sir John Forbes, Ed 1855, p 570

tioned — hyperacidity flatulence, spells of depression, hypochondriasis, together with a number of hysterical symptoms Until nine years ago, however, she was perfectly healthy and her present symptoms, which are identical in all respects with those associated with microcardia, appeared quite acutely after a complete hysterectomy

In Figures 3 and 4 are represented the hearts of two children — a boy 7½ years old with a normal heart, and a girl of 11 years also with normal measurements It is easy to see that the development of the left ventricle has steadily proceeded and that the heart is now no longer of the same rounded figure, the left ventricle and the proportionate development of the auricle having given the heart a shape more like that of the adult heart

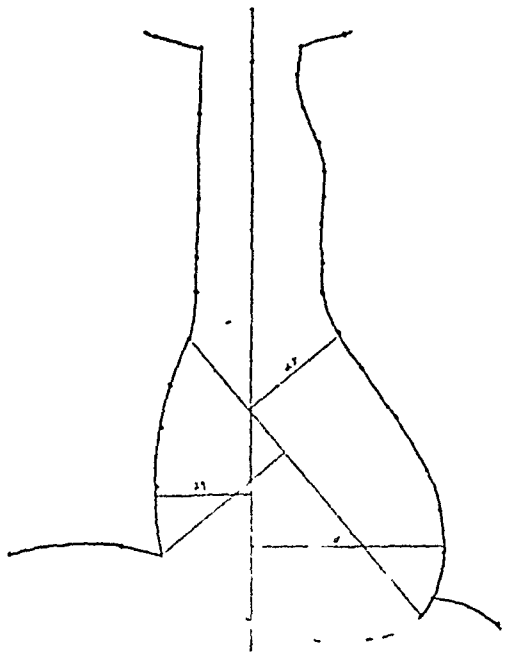

Fig 1 —Normal heart Patient 5 feet, 9 inches tall, weight 130 pounds Blood-pressure, 125 85 (Erlanger) Heart area, 98 sq cm

We now come to a consideration of the abnormally small hearts of the type we have spoken of Figure 5 shows the heart of a man, 35 years old, who has always been more or less sensitive and nervous, with hypochondriacal fears about his health He has considerable hyperacidity and has also had heart attacks which he supposed to be angina pectoris On examination, however, the heart was found to be normal There was an occasional extrasystole and the first sounds at the base were rather feeble and muffled, but there was absolutely no murmur The urine was normal except for a considerable excess of indican He did work equal to a thousand kg in four minutes with but slight increase of pulse and pressure, the pressure, on the whole, being slightly lower than normal — evidently a case of cardiac neurosis The tracing of the heart showed a

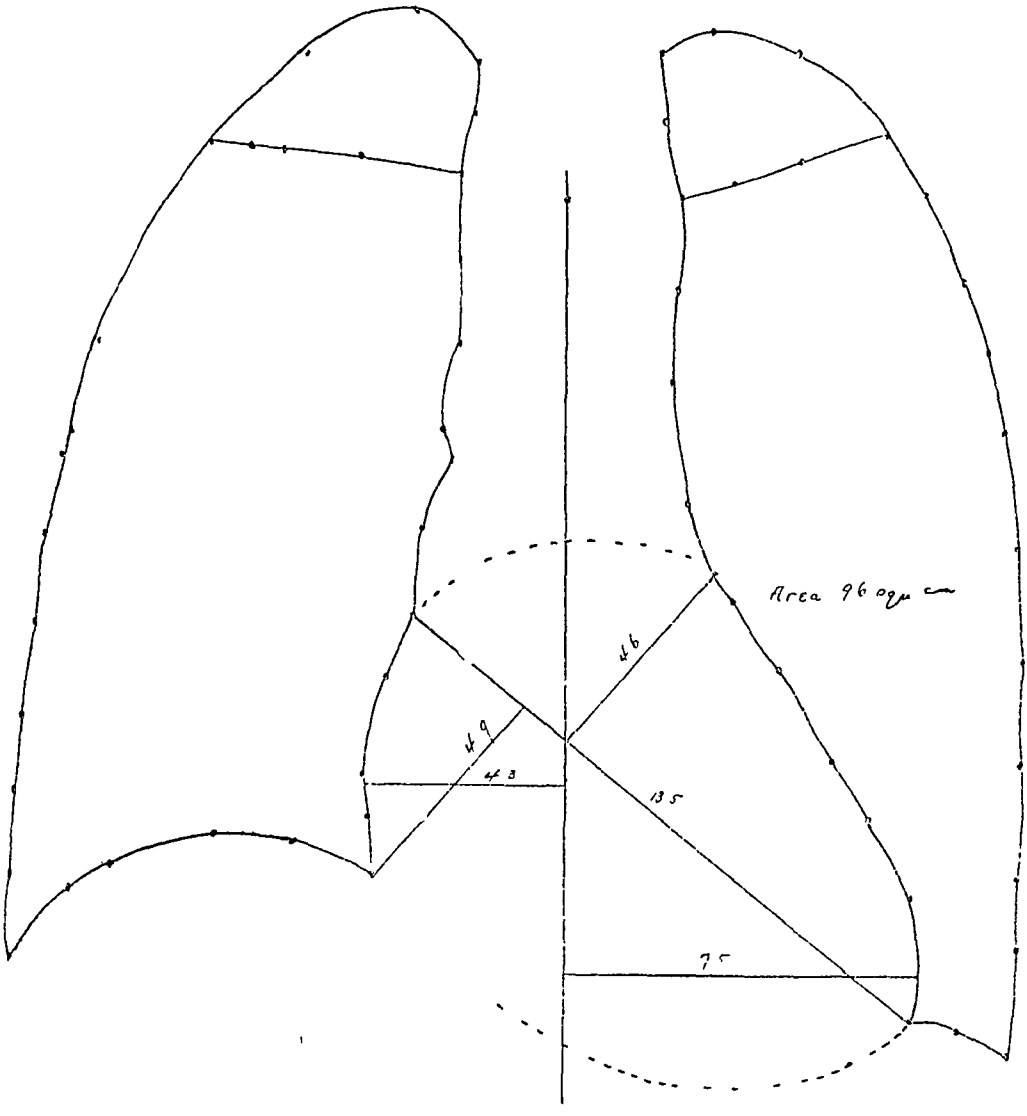

Fig 2—Mrs L, aged 45, 5 feet, 5½ inches tall, weight, 130 pounds Blood-pressure, 130-85 (Erlanger) Artificial menopause, nine years ago All kinds of nervous symptoms Normal measurements

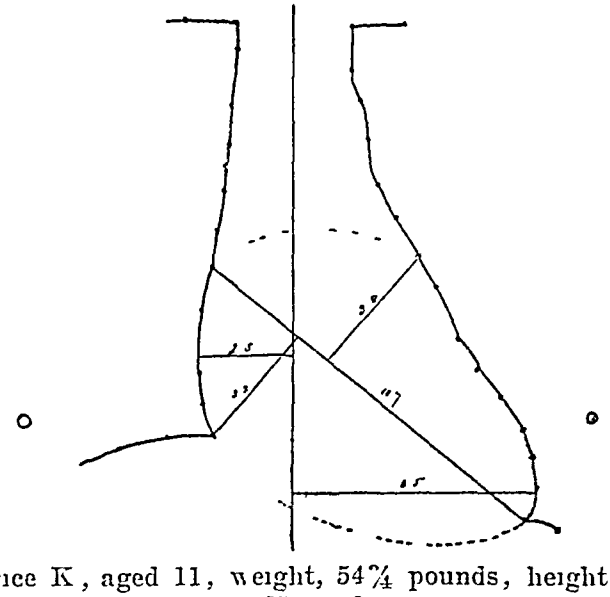

Fig 3—Beatrice K, aged 11, weight, 54¾ pounds, height 4 feet 11 inches Blood-pressure, 100-70 (Erlanger) Normal measurements Area, 57 sq cm

fairly normal aorta but a heart decidedly small as compared with his size and weight

In Figure 6 we have the heart of a young man, 18½ years old, somewhat below weight, with a normal pressure (140-90, Erlanger) He

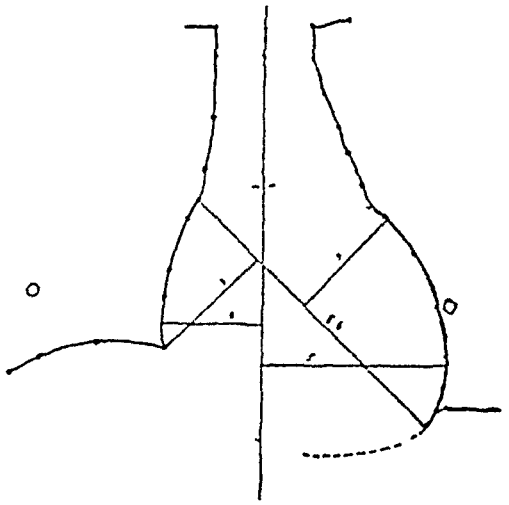

Fig 4.—Richard K., aged 7½, weight 45 pounds, 4 feet tall Normal measurements Area, 45 sq cm

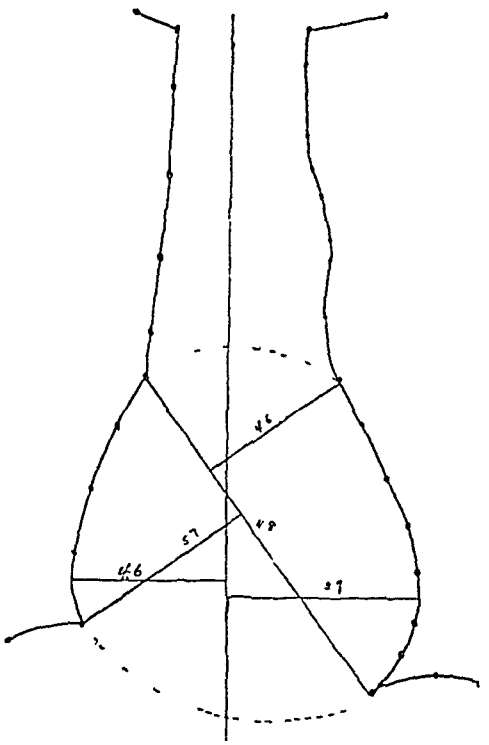

Fig 5.—Male, aged 35 Heart decidedly small as compared with size and weight of patient

has complained for a long time of fainting spells and attacks of dizziness The heart is below normal in all dimensions and the aorta is also very narrow

Figure 7 is from a young man of 21 years, with rather low pressure (140-90, Recklinghausen) He has always been very nervous and suffers

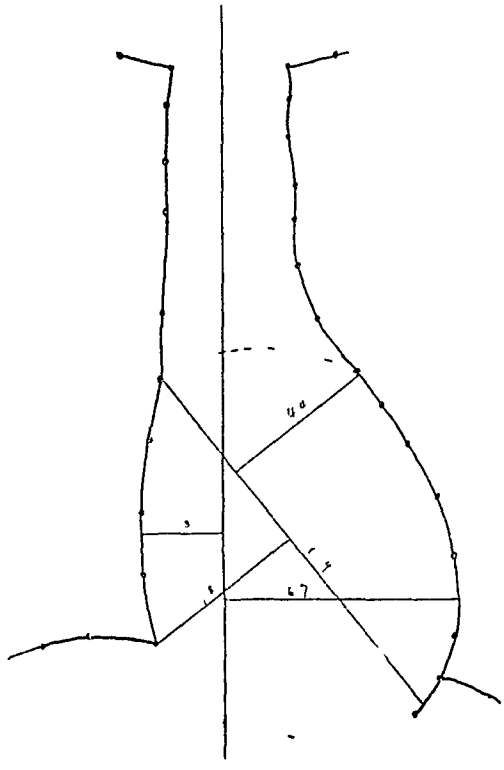

Fig 6—Erick K, aged 18½, weight 109 pounds, height 5 feet 6 inches Blood-pressure 140-90 (Erlanger) Fainting spells, attacks of dizziness All measurements are below the normal Area, 83 sq cm

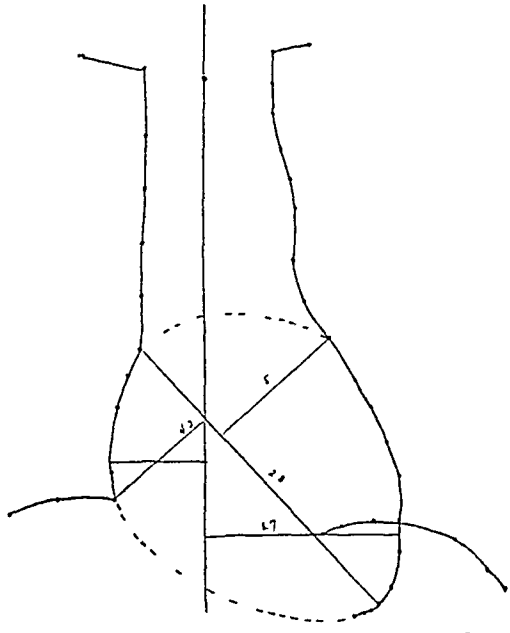

Fig 7—Sam H, aged 21, weight 120½ pounds, height 5 feet 9 inches Blood-pressure 140-90 (Recklinghausen) Neurosis, hyperacidity Mucous colitis Transverse measurements are considerably below normal Area, 82 sq cm

more or less from hyperacidity and mucous colitis In this heart it is the transverse diameter particularly that is too short for a man of his

size and weight The aorta is comparatively wide and the left ventricle well developed, but it must, nevertheless, be classed among the small hearts

Figure 8 shows the heart tracing of a young woman of 26 years who weighs only 105 pounds, pressure 155-95 (Recklinghausen) This heart is below normal in all measurements Besides the ordinary complaints—weakness, hyperacidity, etc —there are distinct stigmata of degeneration in this patient, especially malformations of the hand—rudimentary first phalanges, absence of other phalanges, etc

Figure 9 shows the heart of a young woman, 18 years of age, weight only 91½ pounds, pressure 115-75 (Erlanger), general weakness and

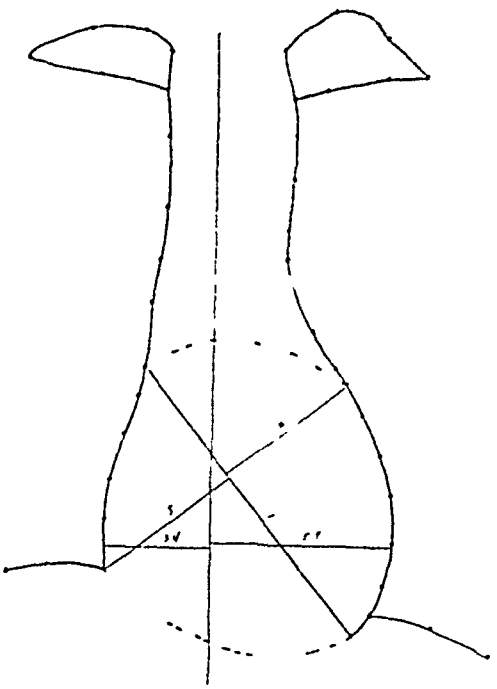

Fig 8—Miss St, aged 26, weight 105 pounds, height 5 feet Blood-pressure 155-95 (Recklinghausen) The habitus malformation of hand All measurements are below the normal Area, 78 sq cm

some anemia A heart distinctly small and below the normal in all measurements

Figure 10, young woman about 18 years of age, 87½ pounds in weight, pressure 108-74 (Erlanger) All measurements distinctly below the normal This heart seems typical of the small hearts in chlorosis, mentioned by Virchow In this patient there was considerable anemia, hemoglobin only 65, reds below 4,000,000 The exceptionally well-marked aorta angusta is also to be seen in the figure

Figure 11, tracing from a woman, 44 years of age, 5 feet 8 inches tall, who has been observed for a number of years She has always been a high-strung, rather feeble, nervous woman, with digestive disturbances,

slight anemia and spells of depression The heart shows a well-developed left ventricle, but the transverse diameter is considerably below normal During an observation of many years, this heart has always remained the same and has shown no signs of muscular insufficiency

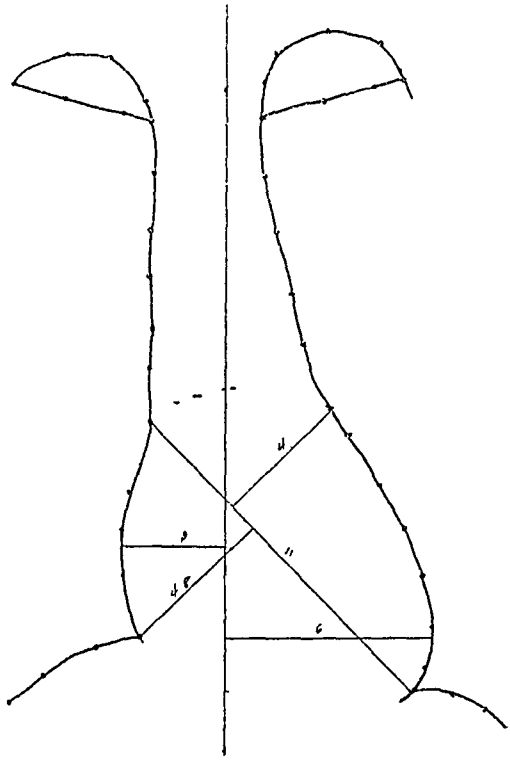

Fig 9 —Miss I , aged 18, weight 91½ pounds, height 5 feet 3 inches Blood-pressure 115 75 (Erlanger) General weakness All measurements are below the normal Area, 65 sq cm

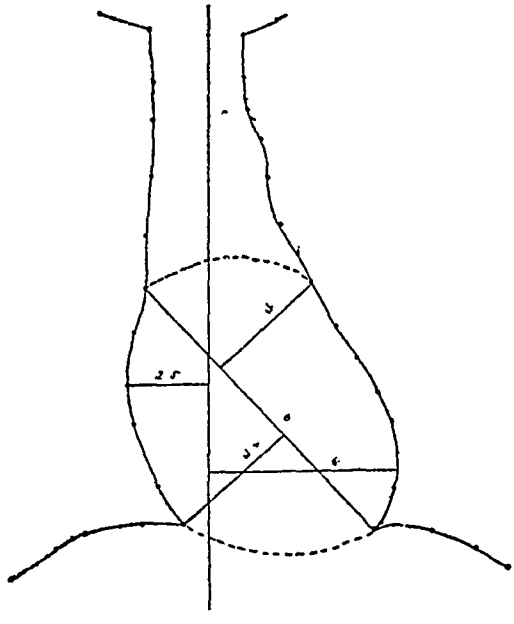

Fig 10 —Miss G , aged 18, weight 87½ pounds, height 5 feet 4 inches Blood-pressure 108-74 (Erlanger) General weakness, anemia Hb 65, red 3,800,000, white, 5,200 All measurements are small Area, 62 sq cm

Figure 12, the case of a girl only 15 years old of poor physical development, who has been backward from earliest childhood At present no sign of menstruation or normal growth of hair, but there are no mental defects This heart is considerably below the normal in all its measurements but does not belong to the cases of microcardia here demonstrated, and is included merely to show the contrast between the congenitally small heart with the clinical syndromes of which we have spoken, and a heart merely badly developed and retarded in its normal growth

We might add many more examples and furnish numerous further illustrations, but we think the few shown will be sufficient to illustrate what is meant

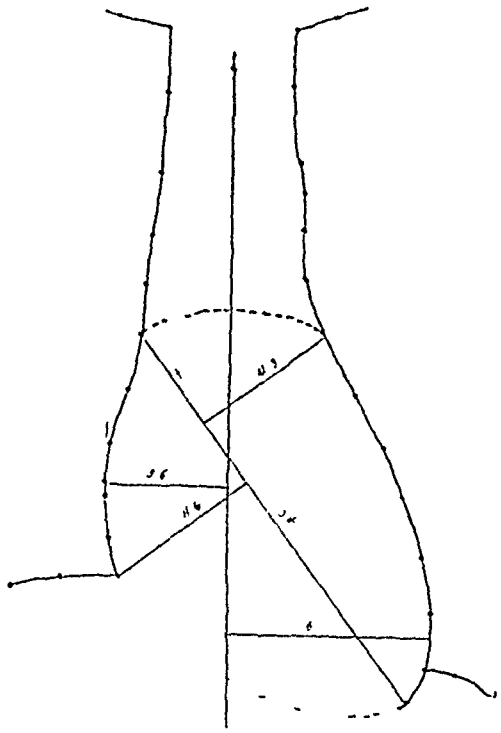

Fig 11.—Mrs R, aged 44, height 5 feet 2 inches High strung, nervous woman Transverse diameter is considerably below normal Area, 85 sq cm

Referring once more to the clinical symptoms in connection with the small heart, there are, as has been stated previously, a great many cases of hyperacidity, flatulence and gas distention, combined with all sorts of peripheral and central nervous affections, which are not associated with the small heart and which differ in many respects from the type which we have attempted to delineate, on the other hand, there are all sorts of transitions and deviations from the typical condition, as just described There may be, for example, little or no hyperacidity, the psychic disturbances may be latent, the peripheral nervous conditions may be very insignificant, or the nervous disturbances may become mani-

fest in some other way the congenitally small heart and the congenitally nervous predisposition will always be present

We wish to reiterate most strongly that we do not for a moment consider this small heart, this microcardia, as in any way the cause of the other symptoms, or even that it constitutes a predisposing factor The small heart is simply one symptom in the entirety of the clinical picture What the cause of the whole may be, what its etiology, we cannot even presume to guess, but we can see in this peculiar combination of a small heart with all sorts of peripheral and central nervous complications a striking example of the correlation to each other of the various organs and functions of the body, however widely separated. It appears probable that the future — possibly the near future — will give us much new and important information on these very subjects The study of

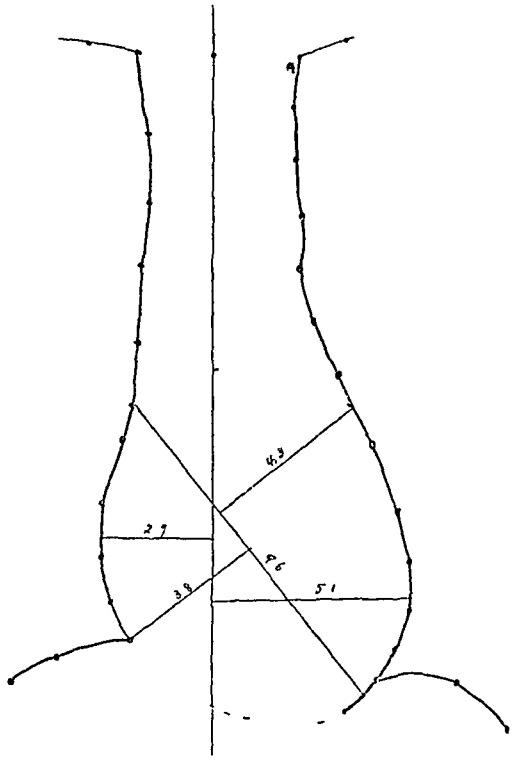

Fig 12 —Esther R , aged 14, height 4 feet 11½ inches, weight 66½ pounds Blood-pressure 110-80 (Erlanger) Poor physical development, no mental defects Measurements, below normal Area, 58 sq cm

the so-called internal secretions and of the chemical and physicochemical forces active along these lines have already led us to conceive of the entire organism as a unit in this sense, that all the organs, all the tissues, all the functions are in some way connected and are continually acting and reacting on each other, under normal as well as under pathological conditions Perhaps in the case of this form of microcardia, also Kraus' view applies — namely, that we have to deal with differences in development and growth, partly ontogenetic, partly phylogenetic, in various parts of the body and strictly correlated to each other

The prognosis as to life in these cases is, of course, perfectly good, as to health it is not quite so favorable It is not difficult to counteract the hyperacidity, and for a long time, perhaps during life, to moderate, if not relieve entirely, the sufferings due to the impairment of the gastric functions It seems true, also, that even without any treatment whatsoever, most of these patients quiet down with advancing years, the irritability of the peripheral nerves the psychic depression, etc, becoming gradually less marked and annoying although these patients will always remain nervous and unable to bear great exertion or physical or emotional strain Many have so far improved in later years as to be considered by themselves as well as by their friends as entirely cured There is even an impression, which of course cannot be proved for a long time, that patients of this type are less subject to arteriosclerosis and other lesions of the heart and blood-vessels

The treatment should in principle be very simple The stomach washings and intestinal irrigations, the administration of powerful and even harmful drugs should be avoided Neither sanatoriums nor rest-cures are, as a rule, advisable A simple, easily digestible but highly nutritious diet, directed as well against the hyperacidity as against the flatulence, should be consistently adhered to, possibly for many years The ordinary treatment of hyperacidity and flatulence — magnesia in its various forms, physostigma, etc — may prove useful The main treatment, however, should be a moral one The confidence of the patient must be gained and held under all conditions and it should be insisted on that relief and cure do not come from drugs, but from a right way of living and from self-discipline in combating the mental depression, etc Life in the open, adequate hydrotherapy, etc along similar lines will also be of service, and these means, while not effecting a cure, may, at any rate, lead to considerable amelioration of the symptoms

Finally we would remark that this type of small heart, having once been sufficiently studied by the orthodiascope, the latter as well as the Roentgen rays in general may be dispensed with The orthopercussion suggested by Plesch and elaborated by Goldscheider, Rumbach and others, if practiced with care and skill, enables the general practitioner to obtain the size and configuration of the heart to all intents and purposes as accurately as through the orthodiascope We have tested both procedures many times in one and the same individual and have found that they tally very satisfactorily

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Virchow Beitrage z Geburtshilfe u Gynakologie, Vol I

THE INFLUENCE OF KIDNEY EXTRACTS ON THE BLOOD-PRESSURE

SUPPLEMENTARY NOTE

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The study of extracts of the kidney is of importance in connection with that phase of the theory of the internal secretion of the kidney which ascribes to such a hypothetical secretion a part in the pathology of those lesions of the cardiovascular system characterized by hypertension In an earlier investigation,[1] I have presented in detail observations indicating that the dog's kidney, unlike that of the rabbit and some other animals, does not contain a pressor substance, and demonstrating conclusively that it does contain a powerful depressor substance which is present also in the urine In view of the fact that the pressor substance of other organs, as for example the adrenal, is constant for all mammals, these observations failed to support the universal application of that phase of the theory of internal secretion which ascribes to the kidney a pressor function

The later observations of Bingel[2] and his associates rendered necessary, however, on account of the method which they employed a reinvestigation of this question

These investigators found that a pressor substance could be demonstrated constantly in the precipitate obtained by saturating the autolyzed kidney extract with ammonium sulphate They worked chiefly with the kidney of the pig but studied also the kidneys of various other animals without, however, special attention to the dog's kidney Their method was as follows

The cortex of pigs' kidneys obtained in a fresh condition from a slaughter-house was washed with salt solution, hashed, ground with quartz sand in a mortar and after the addition of infusorial earth, the juice was expressed under a pressure of 450 atmospheres It was then allowed to autolyze under xylol for from six to fourteen days at a

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From the Department of Research Medicine, University of Pennsylvania, aided by a grant from the Rockefeller Institute for Medical Research

1 Pearce, R M An Experimental Study of the Influence of Kidney Extracts and of the Serum of Animals with Renal Lesion on the Blood-Pressure, Jour Exper Med, 1909, xi, 430

2 Bingel, A, and Strauss, E Ueber die blutdrucksteigernde Substanz der Niere, Deutsch Arch f klin Med, 1909, xcvi, 476, Bingel, A, and Claus, R Weitere Untersuchungen uber die blutdrucksteigernde Substanz der Niere, ibid, 1910, c, 412

temperature of 37 C and, after removal of the suspended particles, was half saturated with ammonium sulphate The fluid obtained after filtration was then completely saturated and the precipitate after dialysis was used for injection into the rabbit

This method applied to the dog's kidney has failed, in my hands, to yield an extract which, when injected into the dog, is capable of producing a pressor effect Extracts of the whole kidney, as of the cortex only, produced no change in the blood-pressure Likewise, if the stage of autolysis was omitted, the extract obtained by complete saturation with the ammonium salt was inert On the contrary, the juice obtained by Buchner press and not autolyzed or treated with ammonium sulphate gave a depressor effect It is evident, therefore, that the method of Bingel, while it removes the depressor substance, fails to demonstrate the presence of a pressor substance This conclusion is not, however, to be regarded as a criticism of Bingel's method, but only as a demonstration of the fact that a pressor substance, if it exists in the dog's kidney, cannot be isolated by the method of extraction which he describes

It has been possible, however, to approach this problem in another way As I have shown elsewhere,[3] the depressor substance normally present in dog's urine frequently disappears from the urine in the severe forms of nephritis caused by uranium nitrate and potassium chromate It was assumed, therefore, that if this substance disappeared from the urine it would likewise be absent from the kidney, and if the kidney contained a pressor substance normally masked by the depressor substance, the pressor substance would under such conditions be demonstrable in the kidney extract Experimental nephritis has therefore been produced by the use of uranium nitrate and potassium chromate, and the urine of the animals, obtained after three to six days, the usual period of disappearance, has been injected daily into normal dogs When the depressor substance of the urine was found to be absent, the animal was killed, its kidney washed free of blood with normal salt solution, and the juice expressed with the aid of a Buchner press

In several very carefully planned experiments, representing uranium and chromium nephritis, it was possible to obtain extracts of the kidney at the time of total disappearance of the depressor substance from the urine, but only two extracts were of value in the study of the point in question, one of these was entirely devoid of depressor action and the other only slightly depressing Neither, however, gave the slightest evidence of the existence of a pressor substance These experiments though few in number, would therefore appear to indicate that the non-

3 Pearce, R M The Depressor Substance of Dog's Urine and Its Disappearance in Certain Forms of Experimental Nephritis Jour Exper Med, 1910, xii, 128

demonstration of a pressor substance in the dog's kidney is not to be explained as a masking of this substance by the more powerful depressor substance The pressor substance apparently, does not exist in the kidney of this animal

SUMMARY

The method used by Bingel and his associates to demonstrate a pressor substance in kidney extracts fails to reveal such a substance in extracts of the dog's kidney Extracts of the kidneys of dogs with experimental uranium and chromium nephritis, prepared at a time when the urine is free of the normally present depressor substance, have no pressor effect.

These observations would appear to demonstrate conclusively that the dog's kidney does not contain a pressor substance which is masked by the more powerful depressor substance They also fail to support that phase of the theory of internal secretion which assumes that the kidney furnishes a pressor substance of importance in the pathology of cardiovascular disease

HEMORRHAGIC DISEASE — SEPTICEMIA, MELENA NEONATORUM AND HEPATIC CIRRHOSIS *

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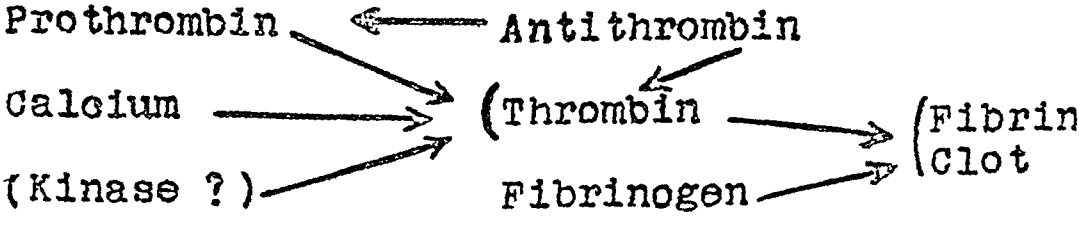
PART I ABSENCE OF BLOOD COAGULATION IN A CASE OF SEPTICEMIA DUE TO THE PRESENCE OF ANTITHROMBIN — A COMPARISON WITH "PEPTONE BLOOD"

Any one familiar with the literature on blood coagulation will realize that not all the factors entering into normal blood-clotting are clearly understood or are explained in various ways by different workers Granting this uncertainty concerning the normal process of blood coagulation, it is not strange that there are more uncertainties and divergencies of opinion bearing on the factors concerned in abnormal or pathological coagulation of blood It seems obvious that we cannot expect to have a satisfactory classification of various hemorrhagic diseases until we have a clear understanding of the mechanism of normal blood-coagulation When this mechanism of coagulation is understood it will be possible to group together many of the indefinite groups of hemorrhagic diseases, hemophilias, purpuras, melenas, etc , according to whether there may be absence of some essential element or presence of an abnormal element having to do with blood-clotting It may be of interest, in the light of our present knowledge concerning blood coagulation, to attempt a classification of some of the diseases associated with a hemorrhagic tendency Perhaps it would be more satisfactory to attempt to group and rename some of these hemorrhagic diseases according to the essential abnormality in the coagulation complex but the clinical names, although unsatisfactory, are established and can scarcely be replaced until a new classification shall be firmly established on a scientific basis It is conceivable that we may talk about a "platelet purpura" or an "antithrombin hemophilia" when it can be shown beyond all doubt that certain hemorrhagic diseases may be dependent on such factors as "platelet" supply or "antithrombin" production or neutralization

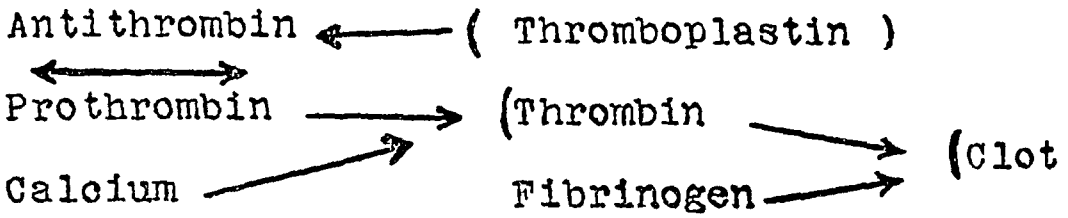
At this point it may be well to indicate in a schematic way the mechanism of normal blood-coagulation



*From the Hunterian Laboratory of Experimental Pathology, Johns Hopkins Medical School

This general plan of blood-coagulation is supported by most of the recent work and one can find an excellent presentation of the whole subject and discussions concerning the various theories in recent articles by Morowitz[1] It is generally admitted that prothrombin requires the presence of free calcium salts for its conversion into thrombin There is some doubt as to whether the kinase is a necessary element in coagulation, but the presence of some such body (Morowitz) seems to accelerate blood-clotting

Howell[2] recently has brought proof that this well-known fact of the acceleration of blood-clotting by tissue juices is due to their neutralization of an antithrombin present in normal blood Howell's theory may be expressed in a schematic way as follows



All the elements of coagulation are present in the circulating blood but the prothrombin is bound by the antithrombin The production of thromboplastin by platelet or tissue injury results in its combination with antithrombin which frees the prothrombin and the coagulation proceeds as indicated The importance of *antithrombin* is much in doubt at present, but it may be an element concerned in normal blood-coagulation and surely plays an important rôle in some diseased conditions Its presence can usually be demonstrated in dogs' blood after an injection of peptone solutions, and it is the active principle of the substance *hirudin* This antithrombin may or may not prevent the formation of thrombin, but does inhibit the union of thrombin with fibrinogen to form fibrin This substance, according to Howell,[2] can neutralize prothrombin and also thrombin after that body is formed

Fibrinogen is a globulin-like body which is present in the normal blood in fairly constant amounts — from 0 8 to 0 2 gm per 100 c c of plasma This substance is removed from the blood *in vitro* by coagulation It forms the body and main bulk of the clot, and is a much more definite factor than thrombin or antithrombin If this substance is reduced in the blood there is no abnormality in the process of blood-clotting, but the formed clot is more or less flabby depending on the amount of fibrinogen This condition in the circulating blood is

1 Morowitz, P Handbuch d Biochemische Arbeitsmethoden, E Abderhalden, 1911, v 223
Morowitz, P, and Bierich, R Arch f exper Path u Pharmakol, 1907, lvi, 115

2 Howell, W T Am Jour Physiol, 1910, xxvi, 435, 1911, xxix, 187

invariably associated with extensive liver degeneration, or insufficiency so the liver may be looked on as one factor concerned in the elaboration of fibrinogen We are ignorant whether or not fibrinogen serves any other purpose except in connection with blood coagulation, but it is possible that this globulin may be available for the nourishment of the tissues Experiments carried out in this laboratory give no support for the view (Nolf[3] and Doyon[4]) that this substance may be used up rapidly after removal of the liver from the circulation No marked drop in blood fibrinogen is observed five hours after the liver has been cut out of the general circulation by means of a preliminary Eck fistula and a secondary hepatic artery ligation As yet our methods of study of these elements of coagulation are crude and we are unable to classify, in a satisfactory manner, many of the hemorrhagic diseases, but it may be of interest to note some of the conditions in which there is abnormal blood-coagulation where the deviation from normal can be recognized

It has been shown by Jacoby,[5] Doyon,[4] and Whipple and Hurwitz[6] that the *fibrinogen* of the blood may be reduced to a very low level (even 1 per cent of normal)) by poisoning with phosphorus or chloroform When the fibrinogen is present in only small amounts in the circulating blood we may observe extensive hemorrhages from small wounds in the skin, oozing from the mucous membranes and purpura This drop in blood fibrinogen is invariably associated with extensive injury to the hepatic tissue, usually with extensive necrosis of the liver cells Recently we have had the opportunity to examine a human being who showed much the same symptom-complex — repeated attacks of purpura, gastric hemorrhages and a slight degree of icterus Examination of the blood shortly after death showed that it clotted in the normal time but the blood-clot was so filmy as almost to escape detection The thrombin and calcium were normal and no antithrombin could be demonstrated Determination of the fibrinogen showed a very small amount (about 6 per cent of normal) and this factor was obviously responsible for the hemorrhagic features of the case The blood could clot but the coagulum was not tough enough to seal the ends of the broken vessels The essential lesion in this case was an advanced cirrhosis of the liver with much degeneration of the remaining parenchyma giving rise to a true hepatic insufficiency

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3 Nolf, P Arch Internat d Physiol, 1905-06, iii, 1, 1910, ix, 407, 1911, x, 37 Estratto d Arch d Fisiologia, 1909, vii, 1

4 Doyon, M Soc Biol, 1905, lviii, 30

Doyon, M, Morel, A, and Policard, A Compt rend Soc biol, 1911, lxx, 92, 1911 lxx, 115

Doyon, M, Morel, A, and Kareff, N Compt rend Soc biol, 1904 lvi, 612

5 Jacoby Ztschr f phys Chem, 1900, xxx, 174

6 Whipple and Hurwitz Jour Exper Med, 1911, xiii, 136

Duke,[7] in recent publications, has emphasized the relation of platelets to many cases of hemorrhagic disease, and has shown that some cases may show a wide fluctuation in the platelet count, but that when the platelet count falls below 5,000 to 15,000 per cubic millimeter, the patient invariably suffers from delayed bleeding-time and may have attacks of purpura, bleeding from mucous surfaces, etc Blood from these patients during such intervals will clot in the usual time in the tissues or in the test-tube, but this coagulation does not close the ends of the several capillaries One can make a reasonable objection to Duke's reports, as he has not followed the other elements of blood-coagulation at the same time with his platelet counts It could be argued with fairness that there could well be a fluctuation in some essential element — for example, kinase or thromboplastin — which could account, too, for the purpura and hemorrhagic symptoms The investigators who choose to look to these elements (the platelets) as the source of one of the coagulation factors would surely raise this question and perhaps with justice It is possible, however, that the agglutination of platelets in these ruptured vessels is essential to *effective* coagulation, and here we have too few platelets to form effective thrombi — the blood may clot but is unable to seal the ends of the severed venules because of this lack of platelets This is somewhat analogous to the condition in chloroform poisoning with very low blood fibrinogen when, also, the blood will clot *in vivo* or *in vitro*, but owing to lack of fibrinogen the clots are very filmy and flabby, quite unable to stop the bleeding and seal the ruptured vessels Duke, working in this laboratory, has been able to show that simultaneous reduction of platelets and fibrinogen experimentally is followed by purpura and prolonged bleeding from small wounds

The abnormal coagulation of blood in certain cases of *jaundice* is of considerable interest and various explanations have been advanced (especially a lack of thrombokinase — Morowitz[1]) In certain cases at least, the blood clots very slowly in contact with the body tissues or even in the test-tube From work done in this laboratory, it seems probable that the *calcium salts* in such cases may be with difficulty available for blood-coagulation King and Stewart[8] have shown that the bile pigments are very toxic and are neutralized in part, by the calcium salts The union of bile pigment and calcium is a pretty firm one and calcium thus combined is only *slowly* available for blood-coagulation, as can be shown by experiments *in vitro* This gives an explanation for the great delay of blood-coagulation in some cases of jaundice in which all the elements of coagulation can be demonstrated to be present Calcium analysis will

7 Duke, W W Jour Am Med Assn, 1910, lv, 1185, Jour Exper Med, 1911, xiv, 265

8 King, J H, and Stewart H A Jour Exper Med 1909, xi, 673

show an excess of this metal, yet it is available only with difficulty because of its union with the bile pigments This observation is in harmony with the well-known fact that administration of calcium salts will lower the coagulation time We do not mean to say that all the cases of jaundice with bleeding are to be explained in this manner, as there seems to be another factor concerned. We hope to report further on this in the near future

Prothrombin, or thrombin, has been found to be present in normal amounts in most hemorrhagic diseases — at least in so far as our present methods permit us to study thrombin or its parent substance prothrombin It is possible that there may be exceptions to this rule, as may be instanced by the report of a fatal case of melena neonatorum which furnished a type of blood that contained normal amounts of fibrinogen and calcium, but would not clot on prolonged standing *in vitro* Nor would it clot even after prolonged contact with the body tissues This blood did not inhibit the coagulation of normal blood, and Schmidt's method by alcoholic precipitation yielded no thrombin The absence of coagulation in this case is due not to the presence of any antithrombin, but to the lack of thrombin or prothrombin This observation is in harmony with numerous observations (Moss,[9] Schloss[10]), that serum treatment is of the greatest value in these cases and may check the bleeding at once Fresh serum, of course, is rich in thrombin

Antithrombin is a substance which has excited a great deal of interest in the past few years, and has been studied in various conditions bearing more or less intimately on the physiology and pathology of the liver For example, Conradi[11] was able to isolate a substance capable of inhibiting normal coagulation, by autolysis of organs obtained with aseptic precautions This substance is very resistant to heat, not destroyed by boiling and is capable of diffusion A similar substance capable of inhibiting coagulation is produced in the circulation during the reaction known as anaphylactic shock, and it is certain that the liver is essential for the completion of this reaction (Nolf,[3] Voegtlin and Bernheim[12]), for if we cut the liver out of the circulation by various methods, we get no drop in blood-pressure and overproduction of antithrombin The best known method of obtaining the antithrombin is by intravenous injection of peptone solution into dogs and cats here, too, the agency of the liver is essential Doyon and his assistants have been able to isolate antithrombin by perfusion of the liver by arterial blood, or peptone blood, and find that this substance withstands boiling, suggesting a close relation

9 Moss, W L, and Gehen, J Johns Hopkins Hosp Bull, 1911 xxii, 272
10 Schloss, O M and Commiskey, J J Am Jour Dis Children, 1911, i, 276
11 Conradi, H Beitr z chem Physiol u Path (Hofmeister), 1902, i 136
12 Voegtlin C, and Bernheim, B M Jour Pharm and Exper Therap, 1911 ii 507

to the substance isolated by Conradi from autolyzed liver-tissue Doyon has also found it in ordinary fresh extracts of liver-tissue Hirudin is a substance obtained from the leach and seems to be a relatively pure antithrombin One must grant that it is highly improbable that all these substances are chemically equivalent, although they have many properties in common, particularly the characteristic of antagonizing the action of thrombin or prothrombin As strong evidence that these various substances are of different nature, we may note that the material (antithrombin) isolated by Conradi, Doyon and his pupils, is a very resistant body, but Howell's antithrombin is very easily destroyed by heat

It is known that in some cases of septicemia there is a delay in blood-coagulation but the explanations are not clear nor simple Some writers suggest the escape of autolytic products into the blood as the causative factor, but it is well known that in pneumonia the blood clots more quickly and firmly than normal Yet in this disease, after the crisis, we have enormous amounts of autolytic material derived from the fibrin, bacteria and wandering cells poured into the blood stream We may argue of course, that in a case of septicemia the system may be flooded with peptones and proteoses resulting from the solution of the tissue and bacterial proteids — that in such a case the body has no adequate means to neutralize the antithrombin which is produced by liver stimulation, and finally, in pneumonia, that we may be dealing with a refractive period which may result in animals following injections of peptone at varying intervals before the final large injection There is little or no weight in the argument that the autolysis of leukocytes in pneumonia frees an abundance of kinase which accounts for the rapid coagulation in this disease, for one can turn and apply the same reasoning to a case of pyemia in which the leukocytes are disintegrating in enormous numbers and yet this blood may clot only after standing for hours The main difference in the autolysis proceeding in a pneumonic lung, as contrasted with the tissue digestion in pyemic abscesses, is that in the former the digestion is proceeding in a tissue rich in blood and affecting leukocytes, fibrin, alveolar epithelium and bacteria In the latter case the autolysis is progressing in tissues shut off, in great measure, from the circulating blood and affecting bacteria and tissue cells, especially leukocytes and relatively little fibrin This difference must account for the wide variation in the blood-coagulation — accelerated in the former case and greatly retarded or quite inhibited in the latter The essential thing is the difference in the *type* of autolysis, for one can be certain that great amounts of autolytic material from bacterial and tissue proteids do escape into the blood circulation in both these diseases It must be admitted that at present there is no adequate explanation for the fact that in some diseases there may be much proteid destruction and absorp-

tion with normal or accelerated blood-coagulation (pneumonia), that in other diseases there may be much the same process going on under slightly different conditions with very abnormal and greatly delayed blood-coagulation It is not easy to explain why blood-coagulation is apparently normal in some cases of septicemia and greatly delayed in other cases But we believe that the following report will show conclusively that, in this case of septicemia at least, there was a very great delay in blood-coagulation due to the presence of a powerful *antithrombin* — a substance capable of inhibiting the coagulation of normal blood

REPORT OF CASE OF SEPTICEMIA

Clinical and Pathological Summary—A strong healthy white man was taken suddenly ill on Oct 10, 1910, with chills, fever and sore throat Several joints became hot and swollen and he was in bed with fever October 22, he became short of breath and had much precordial pain He was admitted to the hospital three days later, very ill, with dyspnea, marked anemia, suppurative tonsillitis, arthritis and pericarditis November 3 blood culture gave growth of *Staphylococcus aureus* and subcutaneous abscesses developed in various regions which yielded the same organism Death occurred Nov 6, 1910

Autopsy, one and one-half hours after death, showed numerous subcutaneous abscesses, purulent tonsillitis, purulent pericarditis with effusion, multiple abscesses in kidneys, prostate and bone-marrow, purulent arthritis The blood removed from the heart is discussed later and that which remained in contact with the body tissues clotted rather slowly and formed flabby clots in from five to ten minutes The abstracts of the clinical history and autopsy report are submitted as they may be of importance in future study and report of similar cases

Clinical History—C V B, white male, aged 19, medical No 26427, was admitted Oct 25, 1910 Died Nov 6, 1910 He complained of shortness of breath and rheumatism The family and past histories were negative The patient had always been well, strong and active Habits were excellent The present illness began suddenly on October 10, with a severe chill and fever The patient noted that his throat was sore and the following morning his right ankle was swollen and tender He remained in bed with fever, headache and bad pains Two days later the right knee became swollen and tender Throat continued sore and swallowing was painful Three days before admission he became very short of breath, pale and cold and complained of precordial pain and was thought to be dying The day before admission he had a second similar attack On admission he complained of pains over the heart as well as dyspnea

Examination—On admission patient appeared very ill Respiration was 48 There was marked anemia of the mucous membranes, no jaundice The throat showed a marked injection with a mucopurulent exudate, the tonsils were inflamed, large and almost met in the midline There were numerous yellow plugs on the surface of the tonsils, no membranes There was a well-marked friction rub over the heart The right knee was swollen, a little reddened and quite tender Red blood-cells 4,600,000, hemoglobin 70 per cent, white blood-cells 23,000, platelets increased in number Differential count polymorphonuclears 84 per cent, large mononuclears 3 per cent, lymphocytes 10 per cent, transitionals 2 5 per cent, October 26, the glands of the neck were easily palpable October 28, the pulse rate continued high and irregular, averaging 130 to 140 per minute Temperature ranged between 101 and 103 F, white blood cells 27 500 October 29, white blood-cells 26,000 October 30 the condition remained about the same with perhaps a little loss of strength October 31 there were no hemorrhages November 1, friction rub was still present November 2 there was evidence of increasing pericardial effusion Red blood cells 5,200 000 white blood-

cells 25,000, hemoglobin 65 per cent November 3 white blood-cells 34,000 General condition was less favorable Several small abscesses were opened on the neck, over the pericardial region and in the left axilla with evacuation of pure greenish-yellow pus Blood culture gave a *Staphylococcus aureus* November 4, white blood-cells 39,700 November 5, white blood cells 35,000 General condition much worse with dyspnea and cyanosis Several other abscesses had developed on the thorax and left arm November 6, cultures made from abscesses showed *Staphylococcus aureus*, while that made from pericardial fluid aspirated remained sterile November 5, culture from aspiration of knee, *Staphylococcus aureus* Urine during the stay in the hospital was negative No sugar, no albumin, negative sediment Blood-pressure was constant, varying between 105 and 115 Temperature curve was uniformly high, 104 F on admission and varying between 100 and 103 to 104 F during the first week November 1, curve began to show some morning remissions, to 101 F with the afternoon rises to 104 or 104 5 F Respirations were continuously high, between 35 and 55 per minute

Autopsy—No 3458 Died 8 50 a m, Nov 6, 1910 Autopsy at 10 30 a m same day Dr Sprunt Anatomical Diagnosis Acute suppurative tonsillitis, *Staphylococcus aureus* septicemia, serofibrinous pericarditis with displacement of thoracic and abdominal viscera and atelectasis of lungs, bronchopneumonia, multiple embolic abscesses in kidneys, prostate, bone marrow of femur and body-wall, acute purulent arthritis (right knee), focal necrosis and central degeneration of liver, cloudy swelling of viscera, hyperplasia of bone marrow, acute and chronic splenic tumor, lymphatic hyperplasia, subintimal fatty degeneration of aorta

The body was that of a well-built, rather poorly nourished, white man There were multiple surgical incisions—abscesses No rigor mortis The body was still warm Livor mortis was present over the back On incision all the blood-vessels, both large and small, bled copiously The blood in the vessels had not clotted in the least, but, after escaping from the vessels and coming in contact with the body-tissues, clotted in from five to ten minutes, forming rather loose clots The peritoneal surfaces were all smooth and glistening On removing the sternum the pericardial sac was found to be enormously dilated, it measured in its lateral dimension about 19 cm On opening the pericardial sac, it was found to be filled with a large amount of cloudy fluid, in which were floating flakes and strings of yellowish-white fibrin

Heart weighed 350 gm Every portion of the heart which was covered by pericardium was now coated with the yellowish-white, friable tissue which on the surface was very shaggy and rough On opening the heart the cavities were found to be somewhat dilated The endocardium presented no abnormality, the heart-muscle was normal

The lungs were both rather heavy and presented a mottled appearance with scattered areas of atelectasis and bronchopneumonia

The spleen weighed 250 gm On section the Malpighian bodies were very distinct, as circumscribed grayish clots of normal size The connective tissue trabeculæ were rather prominent A certain amount of pulp could be scraped off on the knife Stomach and duodenum showed practically a normal mucosa The bile-passages were patent The pancreas was of good size, slightly firmer than normal The lymph-nodes along the pancreas and lesser curvature of the stomach were enlarged, pale gray in color, rather soft and in one place, just above the pancreas, there was one which measured 3 cm in length by 1½ cm in width

The liver weighed 1520 gm, surface was smooth and glistening On section it was pale and rather opaque The lobulation was not well-marked, although a distinction could be made between the darker central and the lighter peripheral portion of the lobule Both adrenals were apparently normal

The kidneys closely resembled each other, they weighed 450 gm The capsule stripped easily leaving a smooth surface of purplish color On the surface were seen scattered here and there small clumps of abscesses measuring from 1 to 3 mm in diameter The cortex measured 5 to 6 mm in thickness, and the striations

were not very conspicuous, but appeared straight and regular The glomeruli showed as minute red dots The little abscesses seen on the surface ran down through the cortex and into the medulla as linear yellowish-white streaks

The pelvic organs were normal except the prostate, which was somewhat enlarged and contained a small abscess cavity about 7 or 8 mm in diameter The trachea and esophagus were normal The thyroid was rather prominent On section colloid was quite conspicuous The lymph-nodes on both sides of the neck were enlarged, rather firm and on section one of them presented a slightly yellowish parenchyma The lymph-nodes in the abdominal and thoracic cavities along the thoracic duct were markedly enlarged and appeared rather juicy Intestines showed to a very slight degree some hyperplasia of the lymphatic tissue, otherwise they appeared normal

The bone-marrow of right femur was pink in color On removal of a piece of bone exposing the marrow, a small amount of an opaque yellowish-white thick fluid was seen to exude from the marrow cavity in the lower half of the femur This soon filled the exposed marrow completely The bone-marrow of the left femur was a dark pink color and of a fairly firm consistence The right knee formed a large fluctuant swelling which was incised, and a large amount of a thick, greenish material evacuated The synovial membrane was swollen and grayish-pink

Microscopical Notes—Heart The heart-muscle cells were normal except for some fragmentation The stroma between the muscle bundles, and associated with the blood-vessels, was loose and edematous and contained a few wandering cells Here and there were found small clumps of wandering cells grouped about, or replacing, a degenerating muscle cell These areas were small and quite infrequent The epicardium was entirely replaced by a thick layer of granulation tissue which was covered by masses of dense fibrin and great numbers of wandering cells

Lungs Some sections showed an extreme grade of atelectasis where the alveolar walls were lying close to one another In such areas, however, were usually found a good many desquamated alveolar epithelial cells or large mononuclear cells The bronchi, as a rule, were filled with an exudate made up of polymorphonuclear and mononuclear cells This same type of exudate mixed with a little fibrin and a few red blood cells was found in some of the alveoli In some parts the lung tissue was practically normal

Spleen The Malpighian bodies were normal The venules were dilated, but their walls were of normal thickness Between the walls of the venules the interstitial cells were quite conspicuous Polymorphonuclear leukocytes were pretty numerous in the lumina of the venules, but not in the interstitial tissue

The lymph-nodes examined all showed the same picture The increase in size was due, in great part, to edema, affecting all the loose connective tissue in and about the glands The sinuses were all greatly widened and full of large mononuclear cells of all types, many of which were actively phagocytic including nuclear particles, red blood-cells and mononuclear cells There was, in addition a great deal of finely granular coagulum and some freshly formed branching strands of fibrin Red blood-cells were not conspicuous, but were present both free and included in phagocytes In some tissue the polymorphonuclear cells were quite numerous The lymph follicles and cords were swollen The cells were loosely packed together, and many large mononuclear cells of a phagocytic type were found in this tissue as well There was some evidence of necrosis

Liver The liver-cells about the portal spaces were swollen but contained large, vesicular, sharply staining, well-preserved nuclei The liver-cells in the central half of each lobule were decidedly smaller Their protoplasm was more uniform and stained deeply with eosin Their nuclei were pyknotic or faintly staining with very indistinct nuclear chromatin In some places there was a true hyaline necrosis with accumulation of polymorphonuclear leukocytes Tiny fat vacuoles were conspicuous The picture was not typical of central necrosis but there was an advanced grade of degeneration with necrosis in some parts and

fatty degeneration and nuclear injury in many of the cells in the central half of every lobule The capillaries in the central portion of the lobules were dilated and contained many wandering cells—polymorphonuclears predominating

The pancreas was normal

Kidney In general the cortex showed an advanced grade of cloudy swelling In certain areas were found small abscess cavities replacing the cortical elements There had been central softening with destruction of the preexisting structures, and the tubules in the immediate neighborhood were dilatd with wandering cells of every description also present in the edematous supporting tissue

Prostate This presents in general a normal appearance, but there was a sharply defined abscess occupying a considerable portion of one section

Stomach All the elements were quite normal

Bone Marrow of Femur There was a marked grade hyperplasia More than half of the section was made up of cell elements which rather obscured the fat cells of the marrow The red-cell elements were rather inconspicuous, although in some areas nucleated red cells were quite numerous The large bone marrow giant-cells were rather numerous The increase of white cells, however, was the striking thing, as one would expect from the picture in the circulating blood In places the marrow almost suggested the picture in leukemia, but eosinophil cells were very inconspicuous The large mononuclear myelocyte with oval or wallet shaped nucleus and the polymorphonuclear cell predominated in all sections In places the marrow was edematous, and here and there was found a delicate reticulum of fibrin with some evidence of cell injury and nuclear fragmentation In places tiny focal necroses were quite obvious, these little areas being made up of ten or twelve injured cells or nuclear fragments included in a mesh of fibrin and fine granular coagulum

Joint Capsule The capsular membrane showed a great deal of edema and its inner surface was covered with granulation tissue

ANTITHROMBIN PRESENT IN HUMAN BLOOD PLASMA

Autopsy 3458 Blood obtained two hours after death November 6, at 10 50 a m Blood from right auricle was collected by pipette into a large flask The blood was still fluid and warm with not even small clots to impede its collection by a pipette

Ninety c c of the blood were mixed with 10 c c of a 1 per cent sodium oxalate solution and centrifugalized to obtain a clear plasma The oxalate plasma was slightly cloudy and opalescent, of an amber color suggesting the presence of bile pigments This is spoken of as "Plasma A" in the accompanying tables The Salkowski test with 4 c c of plasma gave a light green color showing the presence of bile pigments The layer of leukocytes after centrifugalization was very conspicuous and at least three times thicker than normal One hundred c c of blood were allowed to stand in a cylinder giving a good separation by gravitation of the red cells After *two hours* the blood was fluid but a thin film of clot had formed and adhered to the glass after the blood had been poured out into centrifuge tubes This plasma stood in the centrifuge tubes for an hour and again a filmy layer of fibrin formed adherent to the glass wall The plasma was slightly cloudy and of an amber color This is spoken of as "Serum A" because part of the fibrinogen had been removed by spontaneous coagulation

Fibrinogen was determined by a method described previously (Whipple and Hurwitz[6]) and the oxalate plasma was found to contain 0 8556 gm per 100 c c which is somewhat above normal

Calcium was determined in 50 c c of blood and found to amount to 0 00637 gm per 100 c c, which is within normal limits Whole blood that stood undisturbed in a clean flask plugged with cotton showed a filmy clot on the glass after six hours, pretty advanced coagulation after twenty-four hours, with some fluid blood in the center, but complete coagulation at the end of forty-eight hours

Plasma A (Table 1) is the clear oxalate plasma obtained from the human case Plasma D is clear oxalate plasma obtained from a normal dog The calcium lactate solution is 3 per cent in strength

TABLE 1.—EXCESS OF ANTITHROMBIN IN HUMAN PLASMA DELAYS COAGULATION OF DOGS' PLASMA

Plasma A	Plasma D	Calcium Lactate in Drops	Coagulation-Time in Minutes Begin	Complete
	2 0 c c	10	3	5
	2 0 c c	10	3	5
	2 0 c c	3	5	15
4 *	2 0 c c	10	4	8
0 5 c c	1 5 c c	10	4	7
0 5 c c	1 5 c c	10	4	9
1 0 c c	1 0 c c	10	7	17
1 0 c c	1 0 c c	12	8	18
1 0 c c	1 0 c c	10	5	22
1 5 c c	0 5 c c	10	10	22
2 0 c c	0 5 c c	12	5	17
2 0 c c	2 *	10	15	45†
1 0 c c		5	20	60
2 0 c c		15	20	60

*Drops
†Soft clot

Table 1 shows clearly that the normal dog's plasma clots in the normal way on the addition of soluble calcium salts, yet, with the addition of more and more of the human plasma "A," there is found more and more delay in the coagulation-time This shows conclusively the presence of antithrombin

Serum A (Table 2) obtained by centrifugalizing the whole blood from the human subject and pipetting off the clear amber fluid This stood in tubes over night (*not* in contact with the blood-cells), and very filmy clots formed on sides of tubes, but clear amber fluid could be poured off This fluid still contained much fibrinogen and a part of it clotted into a firm mass after standing for twenty-four hours longer Plasma D and calcium lactate solution as used in previous experiment

TABLE 2.—HUMAN SERUM "A" CONTAINS LESS ANTITHROMBIN THAN PLASMA "A"

Serum A c c	Plasma D c c	Calcium Lactate in Drops	Coagulation-Time in Minutes Begin	Complete
0 5	1 5	10	5	10
0 5	2 0	10	5	8
1 0	1 0	10	5	30
1 5	1 0	10	6	20*

*Flabby clot

Serum A (Table 2) had lost a *part* of its fibrinogen by spontaneous coagulation, yet still contained a substance which delayed the coagulation of normal plasma on the addition of soluble calcium salts

Plasma H (Table 3) obtained from a human case of jaundice during life by drawing blood in the usual way into oxalate solution Serum A is described above

TABLE 3.—ANTITHROMBIN INHIBITS COAGULATION OF HUMAN PLASMA

Serum A c c	Plasma H c c	Calcium Lactate in Drops	Coagulation-Time in Minutes Begin	Complete
1 0	1 0	8	13	20
	1 0	4	6	8

The Serum A (Table 3) contained a substance which inhibited the normal coagulation of human plasma on the addition of soluble calcium salts

Serum B (Table 4) *Whole blood* obtained from the autopsy in a clean flask which stood for twenty-four hours with the formation of clots on the sides of the glass, then blood and clots were poured out and centrifugalized, giving a clear amber serum A part of this serum formed only a very filmy clot when allowed to stand for another twenty-four hours and evidently contained only a trace of fibrinogen

TABLE 4.—ANTITHROMBIN SLOWLY NEUTRALIZED BY CONTACT WITH BLOOD CELLS

Serum B c c	Plasma D c c	Calcium Lactate in Drops	Coagulation Time in Minutes Begin	Complete
2 0		10	*	*
1 5	0 5	10	3	6†
1 0	1 0	10	2	5
0 5	1 5	10	2	4
		AFTER AN INTERVAL OF 24 HOURS		
1 0	1 0	10	4	10
‡1 0	1 0	10	4	7

*No clot observed †Small clot ‡0 9 per cent saline

It is interesting to note that the plasma which stood in contact with the blood-corpuscles clotted almost completely after twenty-four hours, while the same plasma standing in clean glass tubes formed only delicate filmy clots The former (Serum B) contained practically no inhibiting substance at the end of twenty-four hours, while the latter (Serum A) *was quite rich in this antithrombin* This would indicate a probable neutralization of the antithrombin by an activity of the blood-cells *in vitro*, the process, however, going on quite slowly

DELAYED PEPTONE POISONING — DOG

This experiment is of so much interest in connection with the human case that it is worth while to report the observations in detail, particularly those concerned with blood-coagulation It will be seen by examination of the tables that the blood from this dog contained a factor

inhibiting the coagulation of normal blood, perhaps more powerful but in every way similar to the inhibiting substance present in the human case

B 23.—Active male mongrel, weighed 20 pounds. The dog was given no food for one week previous to this experiment.

Dec. 13, 1910, at 11 35 a. m., the animal was given intravenously 50 c.c. of a 6 per cent. peptone solution pretty rapidly. The animal was severely shocked, heart beat was very feeble, and pulse not palpable in femoral. At 11 55 a. m. blood was taken from the carotid in the usual manner (130 c.c.). The drawn blood was centrifugalized and a clear slightly opalescent plasma obtained. The layer of leukocytes above the red blood cells was very inconspicuous. This clear plasma did not clot after days, and in fact some of it underwent putrefaction after long standing with never any clot formation. This plasma was used in the tabulated experiments and called "peptone plasma—antemortem."

At 3 00 p. m. (three and one-half hours after the peptone injection) the animal was found moribund. There was bleeding from the gums and from the subcutaneous tissue in the small neck wound. There was a large amount of semifluid feces under the cage and some bloody mucus was present in the freshest feces. The animal died in a few minutes with all the signs of air-hunger.

Autopsy was performed at once within two minutes and very dark venous blood obtained with pipettes from the right auricle. This blood was centrifugalized and showed much concentration of the plasma which amounted to less than two fifths by volume of the whole blood. The layer of white cells was about as thick as normal, speaking strongly for a rapid increase in these cells during the three hours since the first examination. The plasma was slightly opalescent and turbid but no hemolysis was present. This plasma was used in the experiments tabulated below and spoken of as "peptone plasma—Post-mortem." The heart was dilated. Lungs normal. The spleen was mottled with *hemorrhagic areas* up to 2 or 4 mm. in diameter. The liver was much congested and of a uniform deep purple color, the pancreas and kidneys were congested but normal otherwise. The stomach presented a pale normal mucosa, but the *duodenum*, beginning sharply at the pyloric rim, showed a bright red *hemorrhagic mucosa*. No membrane was present but the mucosa was swollen and juicy, full of blood and the lumen was full of bloody fluid containing no clots. This explains the rapid concentration of the blood. This hemorrhagic condition was constant and affected the whole mucosa of the duodenum and jejunum. The ileum showed more of a patchy distribution but scarcely any pale normal mucosa. The cecum and large intestine showed the same hemorrhagic condition. The intestine showed very active peristaltic movements when exposed to the air. All portions of the intestine contained bloody mucus. This remarkable hemorrhagic condition seems to be dependent on the reaction of the fluids bathing it, for the condition is absent in the stomach in which the mucosa is bathed in an acid medium.

Microscopical Sections.—All parts of the intestine showed practically the same picture. The epithelium was intact, and there was no sign of acute inflammation. The proximal half of the mucosa was quite normal, but the distal part showed great engorgement of all the capillaries with rupture in some instances. There was no superficial necrosis. The dilated capillaries contained normal-looking red blood cells with no increase in white cell elements.

Spleen, in general, appeared to be normal. In some areas, however, the spleen pulp contained large amount of red blood-cells. This condition seemed to be a diffuse process, and there was no evidence of any focal hemorrhages with destruction of any of the splenic tissue. There was a good deal of granular pigment included in phagocytes in various parts of the spleen pulp. The Malpighian bodies were large but presented no abnormality. In various parts of the spleen one found fragmented nuclei and cells which appeared to be very actively wandering leukocytes suggesting some cell injury or reaction.

The other organs presented nothing of special interest

Blood Examination.—The peptone plasma obtained a few minutes after the injection of a peptone solution remained fluid for days and no clots ever formed in it. The blood obtained at autopsy from the right auricle remained fluid for six hours, and at the end of twenty-four hours 10 c.c. in a test-tube showed a few filmy clots forming on the sides of the glass and at the surface, much like those observed in the human case but complete coagulation did not follow. After two days there was sufficient clotting to permit inversion of the test-tube without the escape of fluid, but the clot was very flabby. After seven days the same picture obtained, but after ten days the clot underwent autolysis and became quite fluid and hemolysis was very evident. Peptone plasma contained 0.0071 gm. *calcium* per 100 c.c. as determined from 10 c.c.

Cat plasma (Table 5) is a clear oxalate plasma from a normal animal. "Peptone plasma — *ante mortem*" is the peptone plasma obtained twenty minutes after intravenous peptone injection (Dog B — 23). "Peptone plasma — *post mortem*" is the plasma obtained at autopsy immediately after death, three and one-half hours after the peptone injection. Calcium chlorid used in a 2 per cent. solution.

TABLE 5.—PEPTONE PLASMA RICH IN ANTITHROMBIN

Peptone Plasma Post Mortem c.c.	Peptone Plasma Ante Mortem c.c.	Cat Plasma c.c.	Calcium Chlorid in Drops	Coagulation-Time in Hours: Begin	Complete
		0.5	2		7/60
0.5		0.5	6	23/60	38/60
	0.5	0.5	6	36/60	46/60
0.25		1.0	6		30/60
	0.25	1.0	6		30/60
0.5		0.5	3	20/60	40/60
	0.5	0.5	3		3
0.5		0.5		*	*
	0.5	0.5		*	*
1.0			10	†	†
	1.0		10	*	*

*No clot 18 hours. †Firm clot 18 hours.

TABLE 6.—PEPTONE PLASMATA AS USED IN THE PREVIOUS EXPERIMENT (TABLE 5). CAT FIBRINOGEN SOLUTION PREPARED AFTER HOWELL'S METHOD. CAT SERUM, PERFECTLY FRESH, FROM A NORMAL ANIMAL.

Fibrinogen Solution c.c.	Cat Serum c.c.	Peptone Plasma Post-Mortem c.c.	Peptone Plasma Ante-Mortem c.c.	Calcium Chlorid in Drops	Coagulation-Time in Hours: Begin	Complete
1				5	*	*
1	1.0					5/60
1	1.5	0.5				30/60
1	1.5		0.5		2	16
1	1.0		1.0		24	40
1	1.0	0.25			8/60	12/60
1	1.0		0.25		1	13
1			1.0		*	*
		TWENTY-FOUR HOURS LATER THE FOLLOWING TESTS				
						20/60
1	1.0					6
1	1.0	0.5			†	†
1	1.0		0.5			

*No clot. †No clot 6 hours.

Table 5 shows that both the ante-mortem and post-mortem plasmata contain a substance which inhibits the coagulation of normal plasma and that this substance is somewhat more abundant or powerful in the plasma (ante-mortem) drawn twenty minutes after the peptone injection

Table 6 shows that the solution of fibrinogen is free from thrombin and will not clot on the addition of soluble calcium salts, but can be coagulated in five minutes on the addition of fresh serum which is rich in thrombin The peptone plasmata in varying amounts can cause more or less delay in this coagulation of fibrinogen by the agency of thrombin in other words, we are dealing with a substance which is antagonistic to the action of thrombin — an *antithrombin* This substance is more abundant in the "ante-mortem peptone plasma"

SUMMARY AND DISCUSSION — PART I

The case of experimental peptone poisoning in the dog showed the usual picture a few minutes after a large injection of Witte's peptone — great weakening of the heart's action together with a blood which, after removal from the vessels, never clots, and inhibits strongly the coagulation of normal plasma Three hours after this observation the animal was found dying with signs of great air-hunger Blood removed from the auricle would clot spontaneously only after one or two days and was able to delay the coagulation of normal plasma Obviously this second sample of blood contained less of the substance known as antithrombin than did the first specimen Just before death the animal was bleeding from the gums and a superficial skin wound Autopsy showed splenic hemorrhages and a peculiar diffuse hemorrhagic condition of the mucosa of the intestine with much fluid blood in the intestinal lumen We may say this animal presented some of the features of hemorrhagic disease

The human case furnished a blood-picture very similar to that observed in the dog at autopsy Blood removed from the auricle clotted *in vitro* only after a period of one or two days, while in contact with the body tissues, it clotted in from ten to fifteen minutes, which is in harmony with the well-known fact that tissue juices will neutralize the antithrombin Blood-plasma from this case was able to inhibit the coagulation of normal plasma following the addition of soluble calcium salts Fibrinogen and calcium were present in normal amounts Autopsy showed a typical picture of pyemia or septicemia (*Staphylococcus aureus*) with pharyngitis, pericarditis, arthritis and abscesses in subcutaneous tissues, kidneys, prostate and bone-marrow The duration of the disease was four weeks

No purpura was present nor any hemorrhages from the mucous membranes and it may be objected that this case showed no signs of a hemorrhagic disease It may be objected in the same way, that a dog shows

no sign of hemorrhagic disease after an injection of peptone when we know the circulating blood is incoagulable for an hour or more after the injection This condition usually passes off due to a neutralization of the excess of antithrombin, but it may not always do so, as our experiment shows The same experiment shows that after this condition has been present for several hours the animal may develop hemorrhagic symptoms One may argue, then, that this human patient has been suffering from an excess of antithrombin only for a short while and that, had he lived several hours longer, he would in all probability have developed some of the signs of hemorrhagic disease — purpura and bleeding from the mucous membranes

It is much more difficult to explain the mechanism of the antithrombin production in a case of septicemia From experimental data we may assume that the liver is an essential factor in the production of this body It has been suggested that the autolysis of body and bacterial proteids in the body may free substances analogous to peptones and thus call out the overproduction of antithrombin If we grant this possibility, then we have some difficulty in explaining the lack of this phenomenon in pneumonia Probably we will not come to a clear understanding of the question until we understand the mechanism by which the body neutralizes these poisonous proteids and the antithrombin which may be in excess in the blood It may, however, be stated with some certainty that this case of septicemia presented an unusual blood-picture — particularly a great delay in blood-coagulation due to an excess of antithrombin It is probable that further study will show that many septicemias may show a similar blood-picture — particularly those cases associated with purpura and delayed blood-coagulation

PART II PROTHROMBIN ABSENT IN A CASE OF MELENA NEONATORUM

The preceding section gives a review of some of the more interesting factors concerned with blood-coagulation and suggests a possible classification of hemorrhagic diseases according to the factor or factors which may be demonstrated to be abnormal Whether this observation may prove to be a constant finding in cases of melena neonatorum is for future work to decide, but the evidence submitted below seems to show conclusively that the blood from this fatal case was quite free from thrombin or prothrombin A review of the extensive literature on this subject and a discussion of the various theories advanced by the numerous workers is not necessary at this time, for a recent article by Schloss and Commiskey covers these points Some of the more interesting points raised by a study of this case are discussed after the general summary of the blood and anatomical findings

REPORT OF CASE OF MELENA NEONATORUM

Clinical History—M M, colored woman, aged 20, primipara Date of confinement July 8, 1910 Normal pregnancy, labor and puerperium The physical examination was negative

Male child, weight at birth 2,590 gm, length 47½ cm, physical condition excellent The temperature was normal except on the last day of life when it rose to 101 F The bowels moved twice daily July 10, two days after birth, the baby seemed weak and did not nurse well July 11 he was much weaker and did not nurse at all well, breathed with difficulty and the limbs were limp At 8 a m it was noted that the infant was bleeding from the nose, mouth and foreskin, and there was continuous bleeding from the nose from this time until death at 12 45 p m There was no bleeding from the cord The baby had difficulty in breathing, gasping for breath, there was marked jaundice Weight at death was 2,170 gm, the loss of weight had been continuous from time of birth July 8, 2,590 gm, July 9, 2,550, July 10, 2,530, July 11, 2,470 July 12 one bloody stool was obtained The child was given 30 grains of calcium lactate the last day of life

Autopsy No 3405 Baby M, aged 5 days, died July 12, 1910, 12 45 p m Autopsy 3 00 p m July 12, Dr Whipple

Anatomical Diagnosis—Melena, extreme icterus, hemorrhages from nose and large intestine, absence of blood-clots in heart and large vessel, pulmonary hemorrhage and edema, acute splenic tumor

The body was that of a negro male infant 47 cm long Rigor mortis was absent, the skin and subcutaneous tissue, sclerotics and peritoneal fluid were all deeply bile-tinged The body showed no definite areas of purpura anywhere There was evidence, however, of recent hemorrhage from the mouth and umbilicus The subcutaneous fat had a saffron-yellow color The striated muscle was normal, the serous surfaces were all smooth There was a little excess of bile tinged fluid in the peritoneal, pleural and pericardial cavities The heart weighed 20 gm The serous surfaces were smooth Thirty c c of fluid blood were obtained from the right auricle On opening the heart no clots were found anywhere nor in any of the larger vessels The blood was quite fluid throughout all the body The right side of the heart moderately dilated, the intima and valves normal, and the left side of the heart somewhat dilated The wall of the left ventricle averaged 5 mm in thickness The heart-muscle was pale, brownish-red and uniform

Both lungs were edematous and presented a remarkable appearance The anterior portions were pale lemon-yellow, and the alveoli could be easily seen The posterior portions showed a little of this yellow crepitant lung tissue, but the greater part was made up of deep purple heavy lung tissue contrasting vividly with the yellowish tissue Purplish areas were scattered here and there extending up slightly above the pleural surface but not on the cut section The cut section was of similar appearance, it was very moist The bronchi were full of frothy, blood stained material The pulmonary vessels were normal

The spleen weighed 30 gm and measured 7 by 4 by 1 5 cm The capsule was smooth, translucent, rather tense, and the notches well marked The cut section was deep purple in color and very velvety The Malpighian bodies were inconspicuous, the trabeculæ being scarcely visible The pulp was greatly increased in amount, deep purplish in color and scraped off easily on the knife

The stomach contained dark, slimy material The mucosa was pale, quite smooth and uniform, no ulceration was found after careful search Duodenum showed slight injection, an intact mucosa and contained bile stained mucus Pancreas of normal size The lobulation was very clean cut and the organ rather firm the parenchyma being of a lemon-yellow color

The liver weighed 100 gm and measured 11 by 7 by 3 cm The capsule was thin and transparent, and the lobulation normal The color was a deep reddish-brown The cut section was uniform showing the same color and the lobulation pretty sharply marked out No great abnormality except the jaundice tint everywhere The gall-bladder was not dilated and its wall thin The common bile

ducts opened freely into the intestine and bile could be squeezed through it into the intestine by pressure on the gall bladder

The right kidney measured 5 by 2 5 by 2 cm The capsule stripped off easily showing a well-marked fetal lobulation The surface was smooth and yellowish brown in color On cut section the cortex measured 3 mm in thickness The striæ were regular, the pyramids, rather pale, showed no uric acid deposits

Pelvis normal Left kidney of similar description

The adrenals were rather small for an infant but the architecture was normal The outer portion of the cortex was very opaque and yellow, the inner two thirds more translucent and brownish but the medulla relatively inconspicuous The pelvic organs were normal

The small intestine contained throughout thin, mucous material but no blood The mucosa was slightly injected The large intestine showed even more injection but no hemorrhages in the submucosa It contained thin, current red fluid and feces

Neck Organs The pharynx showed superficial ulceration over both tonsils The posterior nares were normal Blood oozed out rather freely from above the hard palate but the region was so small that no definite bleeding-point could be seen The esophagus was quite normal throughout its entire length The larynx and trachea contained a blood tinged, frothy fluid and showed deep, bile-tinging everywhere The thyroid was of normal size, rather pale color and firm in consistence The lymph-glands in this region, at the root of the aorta, in the retroperitoneum and about the celiac axis were all rather large, moist and of a deep cherry red color, some deep purple in color, apparently hemolymph glands The thymus was of normal size and covered the anterior mediastinum well down over the heart The tissue was normal on section except for bile tinging, and the lobulation was quite regular

The line of ossification at the lower end of the femur was quite straight, thin and normal, the bone marrow here of deep purplish-red and the bone marrow of the shaft was very fatty The brain was not examined

Microscopical Notes—Lungs The architecture was regular The bronchi were of normal size and general appearance except for the fact that their lumina were full of red blood-cells with an occasional white blood cell and a good deal of granular coagulum The acini, as a rule, were dilated A few of them contained air, but the majority of them contained either a fine, granular coagulum or great numbers of well-preserved red blood cells The alveolar walls were normal There was practically no exudate of white cells in the alveoli, nor were these white cells particularly numerous in the capillaries of the alveolar walls No meshes of fibrin were made out on ordinary examination of the tissue On careful examination a few of the acini showed some pink-staining, hyaline looking material suggesting rather old compact, perhaps partly digested, *fibrin* A fibrin stain showed that this material gave a typical fibrin reaction This material where present never showed a delicate reticulum seen in fresh fibrin, but had a uniform, hyaline appearance, occurring in small lumps and coarse strands, presenting a rather irregular ragged outline There seemed to be no doubt that this was fibrin In some instances it was surrounded by or intimately associated with large mononuclear cells, possibly a beginning organization In one or two places one could make out strands of this material occupying the pores of Cohn The most careful search revealed no fresh fibrin, and the fibrin which had been deposited obviously was due not to a recent process, but to a process which occurred presumably very shortly after the time of birth This picture was of extreme interest as bearing on the question of blood clotting, for it is obvious that the blood at the time of death was incapable of clotting There was *not* the slightest evidence of any recent clot formation in the alveoli which were full of fresh and well preserved blood-cells and plasma But, obviously, a few days previously the elements for coagulation of the blood and the deposition of fibrin were present at least in the exudate poured out in the lungs from whatever cause It is obvious that the process leading to incoagulability of the blood was not congenital, but developed,

as the clinical history would indicate, during the last two days of life, and in this the histological findings are quite in agreement with the clinical picture

Stomach The mucosa showed a regular structure The villi were normal, no acid cells were seen in the crypts

Small Intestine The architecture and epithelium appeared normal There seemed to be a greater number of polymorphonuclears in the mucosa than normal The blood-vessels were not conspicuous The muscle coats were negative The polymorphonuclear cells were slightly increased in the stroma of the villi and around the bases of the crypts close to the muscularis mucosa Mononuclear cells were decidedly scarce The predominant cell was one resembling a fibroblast

Colon There was a well marked edema of the submucous tissue The vessels of the mucosa were conspicuous, owing to engorgement with red blood-cells The interstitial tissue was rather loose and edematous-looking and contained few mononuclear cells, many cells of the fibroblastic type and a few polymorpho nuclear cells The polymorphonuclear cells were not as conspicuous as in the small intestine The sigmoid showed the same edema of the submucosa, but less congestion of the mucosa Otherwise the picture was identical

The adrenals showed nothing abnormal The cells were well preserved, and the architecture was regular A small mass of chromaffin tissue found at the root of the mesentery was normal in every respect It was associated with a sympathetic ganglion The epithelium and glandular tissue in the pharynx were normal in every respect There was no evidence of any acute inflammation

Thyroid The colloid was not conspicuous, but was present in many of the alveoli It was rather pale staining The epithelium of the alveoli was cubical or high cubical and in places showed some infoldings Many of the acini were small and contained no colloid but presented an active looking epithelial lining The stroma was cellular, loose but not abnormal The vessels were congested

Pancreas The structure was quite regular and uniform The stroma was rather conspicuous and loose The ducts were normal in every respect The acini were made up of normal-looking, glandular epithelium, some of the nuclei being vesicular and others rather dense and compact The islands were discrete, of normal size and made up of sharply staining cells, some of which were quite vesicular, others compact and dense staining There were no foreign cells present

Kidneys The architecture was quite regular and there was no increase in connective tissue anywhere All the glomeruli had a fully developed, mature appearance Some of the collecting tubules contained casts of a pink, hyaline type The glomeruli, as a rule, were normal, but some of them showed a distended capsule of Bowman, the tuft being separated from the capsule by a finely granular coagulum The convoluted tubules in many instances showed a striking deposit of pigment occurring in the basal portions of the cells in fine granules of varying size, the smallest ones just visible, the larger ones being 3 or 4 microns in diameter These larger ones, however, were rather unusual This pigmentation seemed to be limited to the tubules of the convoluted type and was not seen in the collecting tubules The convoluted tubules, as a rule, were dilated as well and contained a frothy or granular detritus The pyramids showed a moderate grade of congestion, otherwise nothing of interest except an occasional hyaline cast

Mesenteric glands presented a normal architecture The germinal centers were not conspicuous The sinuses contained a good many large mononuclear phagocytes including nuclear particles and an occasional red blood-cell In some places one found a good many polymorphonuclears in these sinuses, a condition obviously related to the presence of the same cells in the intestinal mucosa In some places were seen a good many nucleated red cells, some of which were undergoing phago cytosis and an occasional giant cell of bone marrow type is present, and it is possible that there was some blood formation going on in these glands Some of the hemolymph glands contained great amounts of blood particularly in the marginal sinuses Nucleated red cells were numerous here Phagocytes were numerous and contained every type of cell There was some nuclear fragmentation but

this was very inconspicuous In some places polymorphonuclears were rather numerous

Bone marrow of femur The line of ossification was quite normal in appearance with no indications of a syphilitic process The bone-marrow was particularly rich in red blood-cells There was almost total absence of any fat The large giant cells of the bone marrow were numerous and appeared normal No evidence of any necrosis or injury to the marrow could be seen The cell elements stained sharply The striking thing made out was the great number of islands consisting in great part of nucleated red cells Eosinophils and neutrophil myelocytes, however, were quite numerous in some sections No evidence of phagocytosis or nuclear fragmentation could be found

Thymus The lobules and lobes were sharply outlined, being separated by loose edematous stroma The cells at the margin of the lobules were practically all mononuclear cells, but in the centers were found some large mononuclear phagocytes, these were not very striking, however Here and there were found nuclear particles and fragments taking a very deep stain Hassall's corpuscles were very small, usually only 2 or 3 cells in diameter

Spleen The capsule and trabeculæ were delicate The Malpighian bodies were of small size, sharply outlined and made up entirely of lymphocytes The reticulum of the spleen pulp was very delicate The red blood cells were the predominant element, and greater numbers of nucleated red cells were also found In places these nucleated red cells occurred in clumps or islands, as though the formation of red cells was still proceeding into the spleen Large mononuclear cells were not particularly conspicuous Polymorphonuclear cells were present and many of them had the appearance of active migration through the spleen pulp There was no indication of any necrosis or cell injury in any part of the spleen No eosinophil cells were visible The small compact Malpighian bodies would speak strongly against any common intoxication or infection as these lymph nodules react with great rapidity in such conditions

Liver The lobules were of the normal size and arrangement There was no increase in connective tissue The larger bile ducts were normal The liver cells contained a good deal of finely granular, yellowish brown pigment, which, however, was not uniformly distributed being quite abundant in some cells and absent in others The bile canaliculi in places were widely distended with yellow or greenish, hyaline material The nuclei of the liver cells were all well preserved Occasionally were seen a few small fat droplets in the protoplasm of the liver cells The hepatic capillaries were dilated with blood, and many of them contained clumps of mononuclear cells Some of these were obviously nucleated red cells and indicated that the liver was probably taking part in the formation of red blood cells There was an occasional polymorphonuclear leukocyte The Kupfer cells were inconspicuous The liver showed no evidence of any cell injury, but gave evidence of stagnation of bile in the canaliculi and an increase in pigmentation of the liver cells with persistence of the so called blood islands indicating that the liver had not attained complete maturity and was still forming elements of the circulating blood

SUMMARY

The infant was a first child born of a young healthy colored woman after a normal pregnancy The child was in excellent condition for two days after birth, but then began to fail Bleeding from the nose and foreskin began on the fourth day and lasted until death the following day Icterus was well marked One bloody stool was passed

Autopsy two hours after death showed no clots in the vascular system and evidences of hemorrhage in the nasal region and large intestine, into the lungs and spleen There was no evidence of any acute general

infection, nor of congenital syphilis Icterus was present Microscopical sections showed an interesting condition in the lungs The alveoli and bronchi contained much blood and serum, but no fresh fibrin was present Some of the alveoli contained rather dense compact masses of fibrin which obviously had been in contact with the body tissues for some time, as indicated by loss of the delicate reticular pattern characteristic of fresh fibrin This shows that a few days previous to death the tissues were able to coagulate the fibrinogen and form fibrin — a process apparently impossible during the last two days of life Sections from the small intestine gave evidence of a beginning enteritis, instanced by some increase of polymorphonuclear cells in the mucosa The mesenteric glands as well contained a few polymorphonuclear leukocytes in their marginal sinuses The evidences of beginning inflammation here were relatively slight and it seemed difficult to attribute the disturbance in blood-coagulation to this factor The other tissues were negative Study of the line of ossification in the femur and the structure of the pancreas and kidney ruled out congenital syphilis The spleen gave no evidence of any general infection

Blood in contact with the body tissues remained fluid for hours, which excludes the agency of an antithrombin in effecting the non-coagulability of the blood Antithrombin is rapidly neutralized by tissue juices Fibrinogen and calcium were determined and found to be present in normal amounts Thrombin was tested after Schmidt's method and found to be absent Various tests with dogs' blood and plasma gave no proof of the presence of an antithrombin and strengthened the view that the absence of blood-coagulation was due to absence of thrombin or prothrombin

EXPERIMENTAL DATA — BLOOD

The autopsy was performed two and one-quarter hours after death and the heart and vessels found to contain only fluid blood No indication of any clotting could be found in gross even after the most careful search

Antithrombin may be considered at this point and it is evident that it played no important rôle in the absence of blood-coagulation The greater part of the blood was collected in oxalate solution to prevent any clotting, but some blood escaped into the body cavity This blood was perfectly fluid at the completion of the autopsy and the body was placed in the ice-box Twenty-four hours later the blood was found perfectly fluid with not even the smallest clots visible, in spite of the fact that tissue juices neutralize rapidly any antithrombin and can clot "peptone blood," which is very rich in antithrombin This blood remained perfectly fluid after prolonged contact with its tissue juices and this fact alone is enough to exclude any antithrombin as a possible causative factor

in the hemorrhagic condition Further, the same blood which had been in contact with tissues for twenty-four hours was tested against the oxalate plasma of a dog suffering from experimental obstructive jaundice for a period of three weeks ("Plasma J")

"Plasma J" (dog), 1 c c + melena blood, 1 c c = clot — 2 min
"Plasma J" (dog), 1 c c + dilute calcium lactate, 1 c c = clot — 2 min

This observation shows that the melena blood which had been in contact with the body tissues had no more restraining influence on blood-clotting than a dilute salt solution This indicates, too, that the small amount of antithrombin present normally in mammalian blood was neutralized by the tissue juices Study of Table 7 gives indication that the melena plasma (oxalated) still contained a very small amount of antithrombin, sufficient to delay normal coagulation when this melena plasma was very much in excess of the normal plasma

Calcium —This observation shows, in addition, that soluble calcium salts were present in this plasma in considerable amount — sufficient to neutralize the slight excess of sodium oxalate present in "Plasma J" and bring about its coagulation in the normal time

The presence of calcium in normal amounts is shown by analyses given below

Spleen (Melena)—weight 23 gm —Calcium= 00285 gm
Large intestine—washed—weight 7 1 gm — Calcium= 0038 gm
Spleen (normal infant) weight 6 gm — Calcium= 0011 gm

The oxalated blood was centrifugalized and the clear plasma removed with a pipette It was a clear whisky color having a suggestive bile tinge and the froth formed on the surface after shaking had a decided greenish hue indicating considerable cholemia

Fibrinogen was estimated in 10 c c of this plasma by means of a method previously described (Whipple and Hurwitz) and found to be approximately 0 080 gm or 0 800 gm per 100 c c, which is somewhat above normal for healthy adults A parallel determination using "Plasma J" gave almost an identical amount but the accurate amounts in milligrams could not be determined as no accurately weighed filters were available at that time The method, in a word, consists in heat precipitation (58 C) of neutral plasma, collection, desiccation and weighing of the precipitated fibrinogen The determination of fibrinogen shows, however, that there was no lack of this element in the blood of this case of melena

Thrombin was studied by Schmidt's method, which consists of precipitation by twenty volumes of alcohol and after some weeks, extraction of the dried precipitate by water giving a solution of thrombin which will clot readily a pure solution of fibrinogen Normal plasma treated

in this way gives in almost all cases a strong solution of thrombin This plasma (10 c c) was precipitated with twenty volumes of 95 per cent alcohol and allowed to stand for five months The precipitate was collected on a filter and dried over sulphuric acid for several days The dried granular precipitate was divided in half and each fraction treated in an identical manner The first fraction was ground up with a little water and filtered giving 2 c c of a turbid opalescent liquid

0 5 c c of this extract + 0 5 c c fibrinogen solution (cat)=no clot 24 hours
0 5 c c of this extract + 1 c c fibrinogen solution (cat)=no clot 7 days
1 c c fibrinogen solution (cat) + calcium solution=no clot
1 c c fibrinogen solution (cat) + thrombin solution=clot 2 min

This test was performed by Dr W H Howell and I am under obligation to him for many favors and suggestions Three weeks later the second half was extracted in the same way and tested as above

1 c c extract + 1 c c fibrinogen solution (dog)=no clot 24 hours
1 c c extract + 1 c c fibrinogen solution (dog)=no clot 7 days
1 c c fibrinogen solution (dog) + 1 c c serum (dog)=clot 20 min
1 c c fibrinogen solution (dog) + calcium solution=no clot

These tests give strong evidence of the absence of thrombin but it is fair to say that this method fails occasionally to demonstrate thrombin in normal plasma

Table 7 gives additional evidence that this plasma contained no excess of antithrombin but that its non-coagulability was due to absence of thrombin or prothrombin

Plasma (7 c c) was diluted to 30 c c with salt solution — spoken of as "Plasma X" We realize that this dilution was a mistake and that fewer tests with an undiluted plasma would have been more valuable "Plasma J" was obtained from a dog suffering from experimental obstructive jaundice

TABLE 7 —MELENA BLOOD COMPARED WITH DOGS' BLOOD AND PLASMA

Plasma X	Plasma J	Normal Dog's Blood	Calcium Lactate Solution	Distilled Water	Coagulation
c c	c c	c c	c c	c c	
1			0 5		No clot 7 days
1			1 0		No clot 7 days
4		1			80 min
4		2			30 min
3		4			2 min
4	1		0 5		3 5 min
4	1/3		0 5		10 min
1	3*		0 5		filmy clot 3 hours
	4		0 5	4	3 5 min
		4		3	2 min

*Drops

The apparent delay (Table 7) in the coagulation of whole blood by "Plasma X" is explained in part by an excess of sodium oxalate known

to be present, and in part by the small amount of antithrombin normally present in blood The presence of any abnormal amount of antithrombin would have prevented the coagulation of "Plasma J" on the addition of soluble calcium salts, and the slight delay is due to the antithrombin normally present in blood It is seen that appreciable delay in coagulation of "Plasma J" is present only when human plasma (Plasma X) is present in relatively great amounts This observation is in accord with Howell's experiments to show the presence of a small amount of antithrombin in mammalian blood

GENERAL DISCUSSION — PART II

It seems pretty evident that a number of different conditions have been grouped under the heading of "Hemorrhagic Disease of the New-Born" The etiological factors are obviously various and we may expect to find more or less variety in the blood-picture The experimental data in the great majority of the reports are too meagre to be of any value and can be bent in any way to suit the whim of the writer or the theory of blood-coagulation which may be favored

If we accept the theory of Lambert,[13] that in this disease there is a primary blood defect a study of tissue from such a case might give us some hint as to the site of production of the missing element It seems clear that there was such a defect in this case at time of death, and the organs were studied with the greatest care to determine any abnormality which could account for such a defect being congenital We failed to find any congenital defect but did discover that there had been a deposit of *fibrin* in the lung alveoli a few days previously, proving that in this case the defective element (prothrombin) had been present in the blood or tissues at the time of birth In this case, at least, the absence of prothrombin in the blood at time of death was not a congenital abnormality but had developed during the few days of life

Syphilis and septicemia are ruled out in this case by histological study, and it is scarcely possible to harmonize the reports of Lambert Murphy,[14] Schloss[15] and others[16] with such conditions It is impossible to imagine that such marvelous cures could result from blood transfusion or serum injection if the infants were suffering from syphilis or septicemia

Then, again, in cases of septicemia presenting abnormalities in blood-coagulation we may expect to find an excess of antithrombin as the causative factor Some reports of septicemia in infants indicate abnor-

13 Lambert S W Med Rec, 1908, lxxiii, 885

14 Swain, Jacobson and Murphy Boston Med and Surg Jour, 1909, clxi, 407

15 Schloss, O M, and Commiskey, J J Amer Jour Dis Children, 1911, i, 276

16 Moss, W L and Gehen, J Johns Hopkins Hosp Bull, 1911, xxii, 272

mal blood-coagulation and can be explained easily by the presence of an excess of antithrombin in the blood, but these cases do not belong in the group under consideration

It is scarcely conceivable that this condition can be due to any abnormality in the blood-vessels or capillaries as has been supposed by some writers In the first place there is no evidence to support this hypothesis and in the second place it is hard to correlate this theory with the clinical evidence of cure following serum injection

Icterus is a common condition at this time of infant life and can bear no important rôle in the disease There was no sign of liver injury, but a slight grade of bile capillary obstruction as evidenced by small colloid-like plugs in some dilated bile canaliculi

Enteritis was present in this case as shown by the presence of numbers of polymorphonuclear leukocytes in the intestinal mucosa and marginal sinuses of the mesenteric lymph-glands It is possible that this beginning inflammation in this region may be of importance in the causation of this disease, but again this is not a rare finding in infants of this age, and usually associated with no signs of hemorrhagic disease A study of this case, then, offers *no good anatomical evidence* to explain the disappearance of one of the essential factors in blood-coagulation — prothrombin

Thrombin injected into normal animals causes no intravascular clotting, but a response in the shape of an antithrombin production which neutralizes the dangerous excess of thrombin at once It may be argued that injection of thrombin (serum) may bring about a similar condition in these infants and is not a logical procedure But in these infants we are not dealing with a normal organism and circulating blood In normal blood (Howell) the prothrombin is present but anchored by the normal antithrombin present in sufficient amount for this purpose In this case of melena it seems clear that the prothrombin is lacking and this normal balance is absent — it may be said that the antithrombin is not bound or unsatisfied When serum (thrombin) is introduced it is fair to suppose that a necessary part of the thrombin will enter into combination with the unsatisfied or unbound antithrombin normally present and the excess of thrombin will be neutralized in the normal manner Now the equilibrium of the blood, the normal balance of antithrombin and thrombin or prothrombin established, so the circulating blood is in a position to react normally to any injury causing a production of thromboplastin Injury to platelets or tissues can produce thromboplastin which will neutralize antithrombin and permit the prothrombin to combine with calcium and clot the fibrinogen

Published reports of cases treated by blood transfusion or serum injection together with the evidence submitted with this case seem to

prove that certain cases of melena neonatorum show a lack of one of the essential factors of blood-coagulation — namely, prothrombin

PART III FIBRINOGEN GREATLY REDUCED IN CASES OF HEPATIC CIRRHOSIS WITH BLEEDING AND PURPURA A COMPARISON WITH CHLOROFORM POISONING

It is generally recognized that certain cases of hepatic cirrhosis may present signs of intoxication, particularly in the late stages of this disease, and it is believed that these patients are in a condition of hepatic insufficiency and are suffering from a lack of sufficient functioning liver parenchyma Various tests have been devised recently with this very point in mind and may be of certain diagnostic value (for example, the levulose test of hepatic function) Granting then, that we have more or less liver insufficiency in this disease in its late stages, it will be of interest to study some of the elements of blood-coagulation in such cases Experimental work has established pretty conclusively that the liver is an essential factor in the overproduction of antithrombin, best studied after peptone injections In an earlier communication (Whipple and Hurwitz[6]) evidence has been furnished to show that the liver is concerned in the maintenance of the *fibrinogen balance* of the circulating blood and a typical experiment is cited below for the sake of emphasis and comparison with the human cases Given a patient suffering from marked hepatic insufficiency, it seems almost certain that some abnormality in blood-coagulation should be present It seems obvious from the reports submitted below that certain cases of cirrhosis with toxemia, purpura and bleeding do show a great diminution in the blood fibrinogen This blood will clot in the normal time, for all the other elements of coagulation are normal, but the coagulum is very delicate and is unable to check even capillary hemorrhage as the clots are too filmy to seal the ends of the ruptured capillaries It is possible that as more evidence is accumulated it may be found that the fibrinogen may be an index of some value in determining liver injury or insufficiency and may be of some diagnostic importance

REPORT OF CASE OF CIRRHOSIS OF LIVER

CASE 1.—*Clinical History*.—M R W, Hospital No 80108 Age, 54 Admission Oct 8, 1911 Past and personal history negative except for marked alcoholism Alcoholic excess for years Four years ago patient went south where he had a severe attack of malaria At that time he developed ulcers on the shins Five or six months previous to admission the patient showed signs of a changed mental state, of loss of memory and sluggish speech

Examination.—Icterus, palpable enlarged spleen and considerable pigmentation of the skin were present There were purpuric areas up to 3 or 4 mm in diameter, particularly over the legs There was a coarse tremor of the hands, arms and tongue October 8, blood examination showed red blood cells 3,200,000, white blood-cells 5,400, hemoglobin 55 per cent No abnormality noted in bleeding October 11, differential blood-count showed no abnormality Wassermann reaction negative October 17 patient seemed better The urine passed had a smoky color

and contained albumen and red blood-cells October 18 the urine contained a large amount of blood, bleeding of the gums was quite striking Red blood-cells showed a slightly increased fragility to hypotonic solutions October 20 the bleeding time (Duke's method) was over twenty-five minutes, and there was continued oozing from the ear puncture until checked by pressure Coagulation-time tested on the same day was three minutes From October 20 to 22 the patient went into a semicomatose condition from which it was impossible to arouse him

The respirations were slow and deep, suggestive of air-hunger Icterus did not increase in intensity October 22 urine contained numerous red and white blood-cells October 23 the patient was in a profound coma No reflexes, respirations very labored The bleeding from gums was quite free at this time At various times urinary tests for acetone and diacetic acid, reducing bodies, bile and tyrosin negative Temperature was practically normal with a slight rise to 100 F just before death Clinical Diagnosis Chronic alcoholism, cirrhosis of liver, splenomegaly, hemochromatosis, purpura, hepatic intoxication

Autopsy No 3616 Death Oct 23, 1911, 12 25 p m Autopsy October 23, 2 p m Dr Winternitz

Anatomical Diagnosis—Atrophic cirrhosis of liver, collateral circulation established (omentum, parietal peritoneum, diaphragmatic vessels), esophageal varices with rupture, extensive gastric hemorrhage, multiple hemorrhages over the peritoneal surfaces, chronic splenic tumor, ascites, hemochromatosis, pigmentation of face, hands, shins, pancreas and liver, gastric ulcer, jaundice, abscesses in kidneys, bronchopneumonia (slight) and slight fibrinous peritonitis, arteriosclerosis, chronic fibrous pleurisy

The body was that of a fairly well nourished white man, 165 cm long Rigor mortis had not set in, the body was still warm The face, hands and shins were considerably pigmented, deep brown in color The ears were cyanotic, the conjunctivæ slightly icteric The abdomen was slightly distended Both shins were of a bronze color and scarred The skin here was scaly The abdominal fat was scant The veins about the umbilicus in the fat and tissues were distended The abdomen contained about 800 c c of turbid fluid in which flakes of fibrin were seen floating about The peritoneal surfaces were slightly dulled Numerous small petechial pin-point hemorrhages were found over the serosa of the intestine throughout The stomach was considerably dilated and reached almost to the umbilicus These petechial hemorrhages were particularly marked on the parietal peritoneum The liver was beneath the costal margin, the spleen was greatly enlarged The pleural cavities contained no excess of fluid The right pleural cavity was partly obliterated posteriorly by old fibrous adhesions The pericardial sac contained a small amount of deep yellow fluid The pericardial surfaces were everywhere smooth and glistening

The heart was about normal in size The epicardial surfaces were everywhere smooth and glistening The right auricle was normal in size and general appearance except that its endocardium was extremely pale and had a slightly yellowish tinge The tricuspid valves were delicate except for a slight thickening at their free edge The tricuspid orifice measured 12 5 cm in circumference The right ventricle was about normal in size, its musculature was dull and pale The pulmonary valves were delicate, as was also the base of the pulmonary artery The left auricle was small, its walls were smooth The mitral ring measured 9 cm in circumference The mitral valves were somewhat thickened and more opaque than normal The ventricle was small The endocardium was slightly thickened The aortic valves were thickened definitely along the line of closure The coronary vessels were delicate The heart-muscle, on tangential section, was deep brown and homogeneous in appearance

Lungs The left lung was voluminous and pale Toward the posterior portion of the lower lobe it became somewhat hyperemic The bronchial glands were small and deeply pigmented The bronchi contained blood stained mucus Section of the lower lobe showed a pale pinkish-red surface with a few small reddish areas which are slightly elevated and stand up from the surface The right lung was bound

down by firm, fibrous adhesions A few small hemorrhages were to be seen beneath the pleura Otherwise the lung resembled the left

The spleen was large and flabby It measured 17 by 12 by 4 cm The surface was slightly dulled The fibrous tissue did not seem to be in excess The architecture was obscured on account of the great engorgement of the sinuses The Malpighian corpuscles were very small, grayish, translucent in appearance and the spleen pulp soft

Duodenum and stomach were filled with a bloody fluid which was deep reddish brown in color and in large amount It is stringy and apparently contained some mucus When this was washed off, the duodenal mucosa was pale The mucosa of the stomach was of a mottled grayish-red color, and showed on the lesser curvature about 6 cm from the pylorus a small, sharply punched out ulcer which was not more than 1 5 cm in its long diameter and about 0 5 cm deep The base of this ulcer was absolutely clean and the underlying serosa was not thickened

The base of the esophagus showed numerous dilated venules and some small areas where there was definite erosion of the epithelium overlying the venules About 1 cm above the cardia there was a small opening about 2 mm in diameter which readily admitted the blunt end of a probe This extended directly into the dilated venule which ran beneath the mucosa of the esophagus The common bile duct and pancreatic duct were both patent

The pancreas was large, firm and of a rusty brown color On section the lobulation was not prominent The parenchyma had no longer the normal grayish appearance, but it was pigmented a deep brown Some of the lymph glands about the head of the pancreas were similarly pigmented and quite conspicuous

The liver was very small, weighed 1050 gm and measured 20 by 15 by 6 5 cm Its surface presented a characteristic hobnail appearance There were deep brownish elevated nodules and grayish, translucent depressions to be seen everywhere on the surface The gall-bladder was empty except for a few cubic centimeters of thin slimy bile On section the normal lobulation was absolutely gone Fibrous scars ran through the entire liver tissue dividing it into irregular nodules The color of the liver was deep brown There was evidently an increased deposition of iron pigment similar to that described in the pancreas There were ecchymotic specks in some of the islands of liver parenchyma which might have a yellowish or a deep brown, rusty color

Kidneys The right kidney measured 11 5 by 6 by 4 5 cm The perirenal tissue was distinctly icteric The capsule strippel with slight difficulty leaving a surface on which the vascular markings were more distinct than normal The kidney was congested and purplish in color The cortex was regular averaging about 5 mm in thickness The striations were only slightly distorted Some areas showed a few opaque yellow streaks running through the cortex and medulla, outlined by zones of injection—typical abscesses The adrenals were normal

The neck organs were normal

Pelvic Organs The urinary bladder contained a few cubic centimeters of bloody urine Mucosa was normal in appearance, the rectum and prostate normal Aorta was elastic for the most part, but below the renals it become thickened and calcified The common iliacs were elastic and normal in appearance

Intestine The jejunum was very wide, thick and edematous It was filled with a blood-stained mucus The ileum and cecum were normal The bone marrow consisted chiefly of fat

Microscopical Notes—Heart There was well-marked fragmentation of the muscle cells The lungs and adrenal were negative

Kidney Some sections showed small abscesses containing lumps of bacteria, great numbers of polymorphonuclear leukocytes and in places well preserved red blood-cells Other sections showed many collecting tubules filled with hemoglobin, blood and hyaline casts A few of the convoluted tubules contained granular hemoglobin, and others contained well-preserved red blood-cells Other parts of the kidney showed few indefinite scars in the cortex with occasional hyaline

glomeruli The epithelium in many of the convoluted tubules showed a granular or colloid degeneration, but no evidence of necrosis

The spleen presented a typical picture of chronic passive congestion The dilated sinusoids contained a few mononuclear phagocytes and polymorphonuclear cells but chiefly red blood-cells The pulp cells were inconspicuous, and the red blood-cells very scanty in the pulp

The bone marrow of femur in places showed edema, and a few little patches of fibrin associated with occasional necrotic cells The islands of nucleated red cells were conspicuous, and there was considerable hyperplasia of the white-cell islands as well Blood smears obtained from the white-cell layer after centrifugalization showed a good many nucleated red blood-cells

The pancreas presented a diffuse type of chronic induration resembling that present in the liver The deposit of iron-containing pigment was more marked than in the liver The pigment gave the characteristic iron reaction and was found in practically all of the pancreatic acini, and to a lesser degree in the islands

Liver Frozen sections and fat-stains showed scattered patches of fatty degeneration of the liver-cells Many of the fat-droplets were large, but some liver cells contained great numbers of small fat-droplets Some of the lobules showed numerous bile canaliculi which were distended with greenish, hyaline plugs There was a remarkable pigment deposit in the liver-cells This occurred more often in the periphery of the liver lobule, but there was no constant distribution The granules were of varying sizes and all gave a characteristic iron reaction with special stains The general picture was characteristic of the hobnail type of cirrhosis with coarse bands of connective tissue which were much more conspicuous between the lobules, but there was some increase in connective tissue within the lobules The most important feature from the standpoint of this report was the peculiar degeneration affecting the liver cells There were relatively few normal liver-cells Great numbers of them presented this peculiar pigmentary degeneration presented a very glassy, uniform, non-granular protoplasm The nuclei did not stain normally In the center of many lobules were seen very slender atrophic strands of liver-cells indicating some passive congestion and degeneration In a few lobules were seen little patches of hyaline necrosis, but these were inconspicuous There was peculiar granular degeneration of many of the liver-cells which were swollen and very granular, having an indefinite cell outline and poorly staining, atypical nuclei Some of these liver-cells contained small fat-droplets and all were obviously suffering from the action of some injurious agent

CLINICAL AND ANATOMICAL SUMMARY

An adult white male with marked alcoholic history and some mental symptoms presented a characteristic picture of hepatic cirrhosis with pigmentation suggesting hemochromatosis and slight icterus Purpuric patches on legs were present on admission, also anemia but no abnormality in bleeding One week before death bleeding from the gums was noted and blood in the urine Three days later the bleeding time was twenty-five minutes with long-continued oozing of blood from ear-pricks but coagulation-time was three minutes Bleeding from the gums continued and patient went into coma with slow deep respirations and died two weeks after admission

Anatomical Findings Numerous subperitoneal ecchymoses were present The liver was a small hobnail liver showing advanced degeneration of the remaining liver parenchyma There was obvious portal obstruction with esophageal varices and rupture with extensive recent

hemorrhage into the stomach The liver, pancreas and lymph-glands showed a heavy deposit of iron containing pigment — hemochromatosis There was a recent terminal infection as indicated by small abscesses in the kidneys bronchopneumonia and a slight fibrinous peritonitis

EXPERIMENTAL DATA — BLOOD

Autopsy No 3616 Blood was removed from the right auricle one and one-half hours after death while the tip of the auricle was still fibrillating No clots could be found "Serum B," 100 c c dark venous blood, was collected by a clean pipette into a cylinder and allowed to clot A delicate filmy clot formed in from five to ten minutes This was separated with a glass rod, sank to the bottom of the cylinder and no more clot formed at any time After standing for twenty-four hours the clot measured 5 c c by volume Clear serum of an orange-yellow color was obtained by centrifugalization of a part of this blood and was used in the tests given below (Table 8) "Plasma B," 225 c c blood, was collected as above in a cylinder with 25 c c 1 per cent sodium oxalate Centrifugalization gave three-fourths by volume of a clear orange-yellow plasma The froth formed on this plasma after shaking was a faint greenish-yellow tint and bile pigments were shown to be present in small amounts (Salkowski test) Plasma (cat) and serum (cat) were obtained fresh from a normal animal The spleen extract was a concentrated extract (about 30 per cent strength) made with distilled water by grinding up some of the human spleen from the same case Only a few experiments are included in Table 8, but enough to show the absence of any abnormal factor such as a powerful antithrombin

TABLE 8 —COAGULATION IN BLOOD FROM A CASE OF HEPATIC CIRRHOSIS

Plasma B	Serum B	Plasma Cat	Serum Cat	Calcium Chlorid 2 Per Cent	Spleen Extract	Coagulation
c c	c c	c c	c c	c c	c c	
	3				1	no clots
	3				1	no clots
2				0 50		*7 min
		1	1	0 25		7 min
	1	1		0 25		7 min
1			1	0 25		uncertain clot

*Very filmy clot

Plasma B (Table 8), on the addition of soluble calcium salts, clotted in the normal time but formed only a very delicate veil-like clot, exactly similar to the whole blood Serum B formed no clots on the addition of a spleen extract, proving that there had not been an incomplete coagulation as in the case of septicemia in a preceding report, due to an excess of antithrombin Serum B contained no substance capable of inhibiting the coagulation of normal cat's plasma These observations exclude the presence of any abnormal amount of antithrombin

Fibrinogen was determined in two separate specimens as indicated below

Twenty-five c c plasma heated to 58 C for ten minutes centrifugalized washed, collected in a weighed Gooch crucible and dried at 110 C Gooch crucible, dry, 17 5830 gm , Gooch crucible + fibrinogen, 17 5920 gm , Fibrinogen in 25 c c plasma = 0090 gm , Fibrinogen in 100 c c plasma = 0360 gm

Twenty-five c c plasma made faintly acid to litmus with dilute acetic acid, heated to 58 C for ten minutes and treated exactly as the first sample Gooch crucible — dry 17 7610 gm Gooch crucible + fibrinogen, 17 7716 gm Fibrinogen in 25 c c plasma 0106 gm , Fibrinogen in 100 c c plasma 0424 gm

This method was described in detail in a previous communication (Whipple and Hurwitz[6]) Fibrinogen as normally present in human blood averages from 0 800 gm to 0 500 gm Fibrinogen in this case of cirrhosis was greatly reduced, from a normal mean of 0 650 gm per 100 c c to a level of 0 039 gm , which is about 6 per cent of the normal amount This gives a clear explanation of the filmy clots which formed in the blood or plasma tested, for the fibrinogen forms the great bulk of any clot and when it is reduced the clot becomes correspondingly delicate and tenuous

Calcium was determined in "Serum B" and found to be within normal limits

Twenty-five c c Serum B = Calcium — 0 0016 gm 100 c c Serum B = Calcium — 0 0064 gm

Lipase Lipolytic activity was determined in both plasma and serum It was found to be below normal, which speaks against any extensive liver necrosis as well as against much cholemia

TABLE 9 —ACID PRODUCTION BY PLASMA LIPASE AND SERUM LIPASE

,	Plasma Lipase	Serum Lipase
Initial alkalinity	0 05 0 05	0 10 0 10
Butyric acidity	0 10 0 10	0 20 0 10
Total acid production	0 15-0 15	0 30 0 20

Incubation 22 hours at 38 C

The total acid production by ferment activity, causing a splitting of the ethyl butyrate is estimated in terms of cubic centimeters of twentieth normal standard acid and alkali solutions The normal lipolytic activity of the blood may be expressed in terms of twentieth normal solutions as 0 30 c c -0 60 c c This normal ferment activity is greatly increased in obstructive jaundice due probably to the presence of bile in the plasma or serum But there is a much greater increase in ferment activity of the blood after acute liver injury which can be effected by chloroform poisoning and in this condition lipase may be present in amounts ten or twenty times greater than normal

CHLOROFORM POISONING — DOG

This experiment is only typical of many which have been under observation The animal was more susceptible than usual to the drug

Dog 104—April 21 Chloroform anesthesia two hours, 1 ounce given
April 22 The dog was sick and drowsy with much vomiting, bleeding time twenty minutes
April 23 The dog refused food Blood was obtained for fibrinogen estimation (Table 10) Blood clotted in the normal time, but the clot was extremely flabby The animal bled from the small neck wound during the entire day in spite of a bandage which was tied tightly about the neck
April 24 Bleeding from neck continued
April 25 The dog was very weak and pale The neck wound continued to ooze blood drop by drop No clots were seen on the edge of the wound
April 26 The neck wound had stopped bleeding and was distended with soft, loosely adherent blood clots
From April 27 to 30 the animal gained in weight and made a rapid recovery

TABLE 10—(DOG 104) FIBRINOGEN CURVE IN CHLOROFORM POISONING WITH HEMORRHAGE

Date	Chloroform	Fibrinogen gm in 100 c c	Calcium gm in 100 c c	Jaundice	Bleeding
4/16		0 2192	0 0117	—	—
4/21	2 hours			—	—
4/22				(?)	+
4/23		0 0090	0 0133	+	+++
4/26				+	—
4/30		0 6130		—	—

It is certain that this dog was suffering from extensive central hyaline liver necrosis due to the action of chloroform The clinical picture is very like that seen in the cirrhosis case reported above Both dog and man suffered from bleeding from the gums and oozing from small cuts and pricks in the skin Blood-coagulation was normal but bleeding-time greatly delayed and the clots were extremely soft Both acute liver injury and relatively slow liver degeneration can bring about this low fibrinogen content which forces us to the conclusion that the liver is an essential factor in the maintenance of a normal fibrinogen equilibrium The bleeding and purpura in both dog and man are solely dependent on a low fibrinogen content in the blood, as all the other factors of coagulation have been shown to be present in relatively normal amounts

CIRRHOSIS CASES WITH INCOMPLETE DATA

CASE 2—*Patient*—J B, aged 48, with clinical history of alcoholism with occasional attacks of jaundice, vomiting of fresh blood and bleeding from the rectum Red blood-cells 1 700,000 white blood cells 5 300, hemoglobin 16 per cent For several days before examination the stools had been quite black

Anatomical Diagnosis—Cirrhosis of liver, chronic splenic tumor, esophageal and rectal varices, anemia, slight hyperplasia of bone marrow, fatty degeneration of heart chronic diffuse nephritis, acute bronchitis, bronchopneumonia and edema of lungs old purpuric spots

Liver weighed 1,600 gm It presented the characteristic hobnail appearance The connective tissue was conspicuous The islands of liver tissue measured from

1-10 mm in diameter Microscopical sections showed small scattered areas of hyaline necrosis involving areas of from ten to twenty liver-cells The liver-cells contained large amounts of fat which was present in large and small globules Some of the liver-cells showed nuclear degeneration and pyknosis A few of the bile canaliculi were plugged with yellowish-green hyaline material

Blood was removed twelve hours after death, 200 c c were obtained from the right auricle with ease, using a large pipette Blood clots were inconspicuous, but a few very small, rather tough clots were found in the right side of the heart and large veins The serum obtained after centrifugalization was a clear orange-yellow and contained a good deal of bile pigments (Salkowski) Lipase was slightly above normal

Initial alkalinity	0 14	0 15
Butyric acidity	0 68	0 74
Total acid production	0 82	0 89

Incubation 24 hours at 38 C

Case 3 —*Patient* —C L, aged 59, with clinical history of alcoholic excess The patient had been failing for two years before admittance to hospital where he was for four weeks before death, gradually failing with no characteristic symptoms aside from the hepatic and cardiac condition Blood-count was normal except for a slight leukocytosis

Anatomical Diagnosis —Cirrhosis of liver, portal obstruction, ascites, peritoneal adhesions, chronic pancreatitis with fat necroses, chronic passive congestion of viscera, old purpuric spots

Liver weighed 1900 gm The surface was rather rough and coarsely granular, the organ was very tough The cut section showed a coarsely lobulated appearance due to conspicuous fibrous scars and scattered islands of liver parenchyma, from 1 to 6 mm in diameter Microscopical section presented a familiar type of annular cirrhosis causing great distortion of the lobules There was an increase in connective tissue within the lobules in many instances The liver-cells were decidedly abnormal looking Many of them were larger than normal showing huge nuclei obviously hypertrophied There were scattered areas of focal hyaline necrosis with abundant polymorphonuclear leukocytes Great numbers of liver-cells showed a granular protoplasmic degeneration with evidence of nuclear injury The cell membrane was indefinite and the nucleus quite atypical Many of the cells contained large amounts of fat in small or large droplets The whole picture indicated a considerable degree of acute degeneration superposed on the old scarred liver

Blood was removed from the right auricle twelve hours after death and appeared quite fluid No blood-clots were found in any of the chambers of the heart or in the larger vessels After this blood which escaped from the vessels, remained in the pleural cavity for some time a few very small clots were found They were soft and flabby Blood which was collected in a measuring cylinder was examined after some time and found to contain a few small clots amounting to about 10 c c in volume After these clots had contracted and settled to the bottom, there was no further clotting of this serum which stood for several days This serum was of a clear amber color and contained small amounts of bile pigment (Salkowski) Lipase not increased

Initial alkalinity	0 15 0 10
Butyric acidity	0 10 0 10
Total acid production	0 25 0 20

Incubation 20 hours at 40 C

These two cases of cirrhosis present much the same picture as the one reported in detail above and indicate the constancy of this low fibrinogen in cases of cirrhosis with purpura, hemorrhage and intoxication. The elements of blood-coagulation were not studied carefully as in the first case reported, but there is a constancy in these observations which must have some weight in supporting the conclusions. Objection can be made to these last two cases in which the blood was obtained twelve hours after death because some observers claim that there may be autolysis of the blood-clots formed shortly after death. We have never observed this to any marked degree in dogs or human cases when the blood is kept in an ice-chest and believe that it is a negligible factor within the first twenty-four hours when the body is kept at a low temperature.

GENERAL SUMMARY AND DISCUSSION — PART III

A dog severely poisoned by chloroform anesthesia presents a characteristic clinical picture — icterus, bleeding from the gums, prolonged oozing from skin-pricks and cuts, a bleeding-time so prolonged that it cannot be estimated, and obvious toxemia. Such animals may develop purpura and have gastric, intestinal or peritoneal hemorrhage. The essential anatomical change is an extensive central liver necrosis. The blood shows an extreme drop in its fibrinogen content and the other factors of the blood-coagulation are normal. The purpura and bleeding, then, must depend on this great diminution in fibrinogen for the blood-clots are too soft and tenuous to stop even capillary oozing.

Cases of hepatic cirrhosis may show more or less purpura, oozing from the gums, gastric or intestinal hemorrhage, and delayed bleeding-time, particularly when suffering from the so-called "hepatic toxemia." Here we are dealing with a relatively slowly developing hepatic insufficiency, while in the animal experiments there is an acute liver injury with more or less insufficiency. Yet the clinical pictures have many points in common. Blood from the cirrhosis cases shows a very low fibrinogen fraction, but other elements of coagulation are normal as in the dog experiments.

The hemorrhagic symptoms in this group are surely referable to this drop in blood fibrinogen and dependent on it alone. The blood clots in the normal time but the clots are too soft to close the ruptured vessels and bleeding continues. This observation is of interest in connection with one explanation of "purpura" as referable to increased fragility or delicacy of capillaries. We cannot imagine any such fluctuation in capillary fragility in this condition (acute or chronic) yet just as soon as the blood fibrinogen drops below a certain level we may observe purpuric spots. It is obvious that after trauma we may have a subcutaneous extravasation of more or less blood in a normal person. It is quite

possible that *slight* bruises may rupture a few capillaries which would give rise to no visible extravasation in normal persons, but could be associated with much blood extravasation in these cases in which the blood-clots are too soft to close the broken vessels This is surely a possible explanation for the purpuric spots observed in these cases and may be applicable to other hemorrhagic diseases in which other elements of coagulation are abnormal

Observations on dogs suffering from acute liver injury (chloroform) with hepatic insufficiency and parallel observations on human cases of cirrhosis with progressive hepatic insufficiency prove beyond any doubt that the liver is an essential factor in maintaining the normal fibrinogen balance of the blood It is possible that the fibrinogen is elaborated by the liver, but more evidence must be submitted to establish this point

At present it is difficult or impossible to get an accurate estimate of liver efficiency but it is possible that the fibrinogen curve may prove of some value in diagnosticating a true hepatic insufficiency, resulting from either acute intoxication or chronic progressive degeneration The accurate determination of blood fibrinogen is not suitable for clinical purposes, but in cases with very low fibrinogen, this fact is obvious from examination of the blood-clots in a small test-tube Better still, a little oxalated plasma can be obtained and clotted by means of calcium salts giving a pure clot without blood-cells from which a rough estimation of fibrinogen is possible

BOOK REVIEW

THE PARASITIC AMŒBAS OF MAN By Charles F Craig, M D, Captain, Medical Corps United States Army From the Bacteriologic Laboratory of the Army Medical School, Washington, D C, and the Rockefeller Institute for Medical Research, New York Cloth Price, $2 50 Pp 253 Philadelphia J B Lippincott Co, 1911

Captain Craig is well known as one of the most persistent, as well as accomplished, students of intestinal amebas He was the first to confirm the important discovery of Schaudinn By reason of his assignments to the most important stations in the United States and its territorial possessions, he has been able to study intestinal amebas under peculiarly favorable conditions and his accuracy as an observer, combined with his great technical skill, have given him exceptional advantages A book on the subject by him must, therefore, be a matter of more than ordinary interest Careful study of the work named above shows that the result is highly satisfactory Captain Craig has given us a full and concise account of amebas in their various relations He begins with a brief but adequate historical sketch, the salient features of which are the facts that intestinal amebas have been known for just half a century and that more work has been done on them in the last ten years than in all the time before The chapter on "Morphology and Biology" makes clear that there are many species of intestinal amebas, but that few of them are pathogenic The chapter on "Cultivation and Nomenclature" is a very sensible and satisfactory one, and one that would be useful for the beginner in any line of protozoan investigation The chapter on "Technic" is clear and practical Captain Craig emphasizes the necessity of using fresh preparations for diagnostic purposes As he says, stained preparations should never be depended on for diagnosis, except in the hands of an expert The chapter on "Cultures" emphasizes the fact generally accepted by zoologists that none of the amebas that are parasites of man have been cultivated The bulk of the book is given over to the more important species, *Entamœba coli*, *Entamœba histolytica* and *Entamœba tetragena* This gives a complete picture of our present knowledge of human amebiasis, and its careful study should greatly advance our knowledge of all problems connected with intestinal amebas It should be impossible for anybody who carefully reads the book to make a diagnosis of amebic colitis by finding after many hours search a single possible ameba Briefer but adequate treatment is given to other forms of amebas that have been found by investigators in various parts of the world, including the interesting *Paramœba hominis* Other chapters describe amebas found in the mouth, in the genito urinary tract, in exudates, abscesses and in the lungs

A large, though necessarily incomplete, bibliography is included The mechanical execution of the book is good, the illustrations are well chosen and successful, and altogether the book is one that cannot be neglected by any student of protozoa or of intestinal diseases

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LINGUATULA SERRATA (LARVA) IN A NATIVE CENTRAL AMERICAN*

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Two cases of infection by linguatulids have been observed at Ancon Hospital during the past six years and while the condition is not uncommonly met with at autopsy in Europe, and infections by other representatives of the *Linguatulidæ* — *Porocephalus armillatus* and *moniliformis,* have been reported from Africa and Asia, the literature appears to afford no example of an infection by *Linguatula* in a native of America

The case reported by Aitken[1] was one in which *Porocephalus armillatus* was found in the lungs and liver of an African negro soldier who died about eight months after leaving Africa "Although in this instance the negro was stationed in Jamaica, it is most probable that he had the germs of these parasites within him when he left his native shores in some part of Africa, and that this parasite is endemic neither in St Helena nor in Jamaica"

Case Report —In the case reported here a post-mortem examination was being held on the body of Leonidas T, aged 32, a native of Nicaragua He had been in Guatemala fourteen months previously and had lost an arm during one of the revolutions there It cannot be ascertained with accuracy how long he had been in the Canal Zone, for he was not an employe He entered the hospital at Paraiso and had evidently been on the trails for a couple of days (Dr Preston) The patient was transferred to Ancon Hospital Aug 29, 1911, and died September 15 During the autopsy, immediately after the lungs had been removed and incised, a larva was found crawling over the cut surface and along the pleura As this was the only larva found, its exact location during the life of the patient is not known It may have been free in the pleural cavity encysted in the lungs or free in a bronchus A very careful search was made through the accessory nasal sinuses pharynx, lungs, bronchi, and other cavities and viscera, but no adults or other larvæ were found

The larva, while parasitic was, no doubt harmless and played no part whatever in the cause of death, which was cirrhosis of the liver

Sections of the liver contained no evidences of encysted dead or calcareously infiltrated parasites and no evidence of their ever having been present

Description of Larva —The larva was active and crawled about very much like a fly larva Its activity was retained after being five or six hours in saline solution under a coverslip Its color was white, becoming gravish and translucent

*From the Board of Health Laboratory

1 Quoted from Sambon Jour Trop Med and Hyg Lond 1910 xiii, 212

when mounted temporarily under a cover slip with saline solution The body is 6 5 mm long, its greatest breadth 1 52 mm , it is flattened and tapers to an obtuse point posteriorly It is encircled transversely with alternate rows of pores and retrorse colorless, chitinous spines These rows of spines are ninety two in number and are about 0 072 mm apart and each spine is about 0 036 mm long The first or anterior, row of spines encircles the mouth and is inserted higher at the sides and dips ventrally so that at the sides it is 0 184 mm from its neighbor The pores are absent between the first and second rows of spines The fourth and fifth rows of spines are incomplete, ventrally in a line posterior

Fig 1 —Larva of *Linguatula serrata*, measuring 6 5 mm × 1 52 mm , found at post-mortem examination of the body of a native of Nicaragua

to the mouth The anterior end of the larva is broader than the posterior end and its anterior margin is 0 288 mm in width The mouth is subterminal, elliptical in shape, and reinforced with chitin The anterior margin of the mouth is 0 2 mm posterior to the anterior margin of the larva The anteroposterior diameter of the mouth is 0 136 mm , the transverse diameter is 0 080 mm At each angle formed by the junction of the anterior margin with the sides of the larva is a stigmal pore (?) which communicates with the interior by a narrow canal Surrounding the mouth are two pairs of strong, jointed, chitinous hooks, the

jaws of the anterior pair are opposite the oral aperture The second pair are placed a little posteriori to and more external than the first The anterior portion of the hooks is very sharp and may be protruded through slits or invaginations in the integument of the larva The hooks are 0 576 mm long As the anterior portions of the hooks are retracted, the convexities of the free, sharp-pointed tips fit into short chitinous protective sockets or grooves After watching the movements of these chitinous hooks it is seen that the anterior jointed ends with their very sharp points have a hammer-like action and are projected and retracted by a prehensile movement very much like that of a cat's claws The impression received at first is that the hooks correspond to the terminals of legs They are not legs, however, but should be regarded, as has been pointed out by Dr Stiles, as homologues of the mandibles and palpi of *Arachnida*

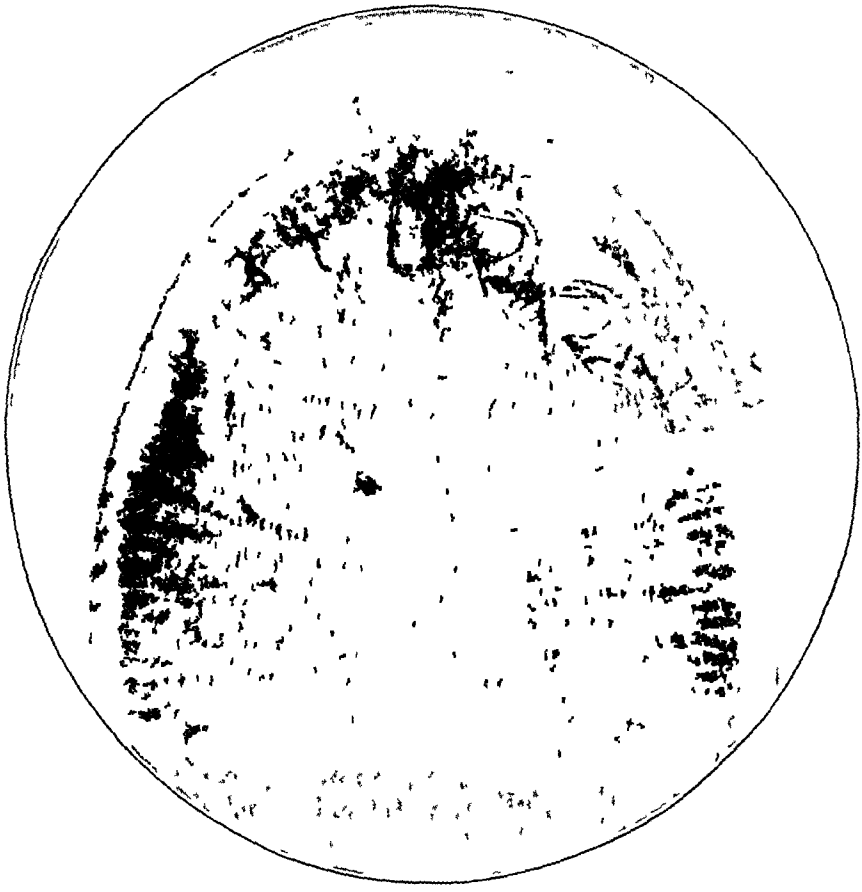

Fig 2—Anterior end of *Linguatula serrata* larva shown in Figure 1

In 1905 one of us (S T D) saw, in a film preparation from a stool, a larva very much like the one just described The chitinous retrorse spines and the chitinous hooks around the mouth were darker in color than in the case described above, but otherwise resembled it closely

It is believed that the patient was a white man, either a native of or long resident in Central America

The *Linguatulidæ,* or tongue worms, belong to the phylum, *Arthropoda,* class, *Arachnida,* which includes the spiders, mites, ticks etc By reason of their peculiar parasitic habits, they have an appearance very unlike most members of the class The sexes are distinct, the males of *L serrata* (Frolich, 1784) being from 18 to 20 mm in length and white

in color The female is of a yellowish color, from 8 to 13 cm long Eggs are laid and from each egg there hatches out a four-legged larva with rudimentary mouth parts The female lives in the nasal cavities of carnivora and is said to lay as many as half a million eggs, which pass out of the nasal cavity mixed with nasal mucus and are deposited on pastures where they are taken up by grazing animals The larva, which resembles a mite, pierces the mucosa of the intestinal tract in the new host (herbivora) and makes its way to the mesenteric glands, liver, kidney, etc, where it becomes encysted

During a period of about six months the larva undergoes metamorphosis into the nymph, which exhibits many of the characters of the adult Later, complete development of the adult takes place, in a primary host

Pathology in Dogs—The pathological changes, according to Friedberger and Frohner,[2] are not serious and consist of a catarrhal condition or rarely a hemorrhagic infiltration of the mucosa of the ethmoidal cells and nasal passages

In man, Landon[3] reported a case of infection in a "blacksmith, in which there were pains in the liver, accompanied by icterus and intestinal disorders Later, when symptoms were reduced to icterus and weakness, bleeding of the nose set in and continued with slight intermissions for seven years An unpleasant sensation of pressure in the left nasal cavity set in with inflammatory swelling of the mucous membrane At last, when the pressure in the nose had considerably increased, a *Linguatula* was expelled from the nose with a violent attack of sneezing The bleeding then ceased and the patient soon recovered"

Braun[4] is of the opinion that the first illness was connected with the invasion of the liver by numerous larvæ which disappeared after encystment One or a few of these must have subsequently found their way to the nose and settled there

Incidence—The adult of *L serrata* is more rarely found than the larval form The adults are found most frequently in dogs and wolves chiefly in their nasal cavities, and frontal sinus, and in the central nasal passage, also the ethmoidal cells, pharyngeal cavity, in the larynx, behind the rima glottidis and in the middle ear The larval form is found most frequently in sheep, also in oxen, hare, rabbits, deer, dromedaries, raccoon, antelope, swine, guinea-pigs and also in man, in whom it occurs encysted in the mesenteric lymph-nodes, liver, kidneys and lungs, and also free in the abdominal and pleural cavity (?) and air-passages

2 Friedberger and Frohner Veterinary Pathology, London, Hurst Blackett, 1908, ii, 21

3 Landon Berl klin Wchnschr, 1878, xv, 730

4 Braun Animal Parasites of Man, New York, 1906, William Wood & Co

In man· Virchow found the parasite in Wurzburg and Berlin, Wagner in Leipsic, Frerichs in Breslau, five times in forty-seven autopsies Zenker first called attention to the occurrence of the larva in man, having found it nine times in the liver in 168 autopsies According to Zaeslin, two cases occurred in Basel in 1,914 autopsies At Kronstadt larvæ were found six times in 659 autopsies, most frequently one or two specimens being found in the liver

In dogs Friedberger and Frohner state that the parasite is found more commonly in some districts than in others They found it frequently in Berlin but only exceptionally in Munich Heiing found it once only in Stuttgart, while Colin found it in sixty-four out of 630 Parisian dogs examined The parasite seems to be present only in the larger breed of dogs, such as mastiff and the butcher's dogs, and was found oftenest in the ethmoidal cells firmly attached to the mucosa

BLOOD-PRESSURE IN CHEYNE-STOKES RESPIRATION

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Special impetus to the study of this particular physiological feature has been given by the work of Cushing,[1] who showed experimentally and clinically that in Cheyne-Stokes respiration associated with increased intracranial tension the blood-pressure was low during the period of apnea and high during the period of hyperpnea J A E Eyster[2] demonstrated the clinical value of this fact in the differentiation of Cheyne-Stokes respiration associated with increased intracranial tension from other types The great interest and importance of this observation justifies a report based on fifteen cases of Cheyne-Stokes respiration arising from various causes, including cerebral hemorrhage, cerebral and general arteriosclerosis, myocarditis, decompensated organic heart lesions, pneumonia, infarct of the lungs and nephritis The tracings were obtained by the Erlanger sphygmomanometer with a pneumograph attachment

TABLE SHOWING BLOOD PRESSURE IN FIFTEEN CASES OF CHEYNE STOKES RESPIRATION ARISING FROM VARIOUS CAUSES

No	Name	Clinical Features	*Blood-Pressure During Apnea*
1	N	Apoplexy, auricular venous pulse	Low
2	T	General arteriosclerosis, myocarditis, extrasystoles	High
3	W	Mitral insufficiency, *positive venous and liver pulse*	High
4	B	Mitral and aortic insufficiency	High
5	H	*Pneumonia, auricular venous pulse*	Low
6	B	Mitral insufficiency	High
7	L	Cerebral arteriosclerosis and nephritis	High
8	R	*Tic douloureux, (asthma?)*	High
9	L	Cerebral arteriosclerosis (Traube Hering waves)	High
10	S	Pseudobulbar palsy, tachycardia	Low
11	C	Infarct of lung, nephritis	High
12	H	Mitral insufficiency	High
13	J	*Fractured hip, arteriosclerosis*	High
14	B	Pneumonia, normal venous pulse	High
15	A	Apoplexy pseudohemisystole	Low

From this table it can be seen that the findings corroborate Eyster's observation with one exception, Case 5, one of pneumonia with no neurological findings and no organic lesion of the heart *Post-mortem* examination was not obtained

1 Cushing Am Jour Med Sc, 1902, cxxiv 375, 1903 cxxv, 1017, Johns Hopkins Hosp Bull, 1901, xii, 290

2 Eyster, J A E Johns Hopkins Hosp Bull 1906, xvii, 296

In Cheyne-Stokes respiration of increased intracranial tension it was seen that the blood-pressure began to rise slightly before respiration commenced, being highest as the summit of respiratory movements was reached, when it began to fall, reaching its lowest point during apnea In cases not associated with increased intracranial tension the blood-

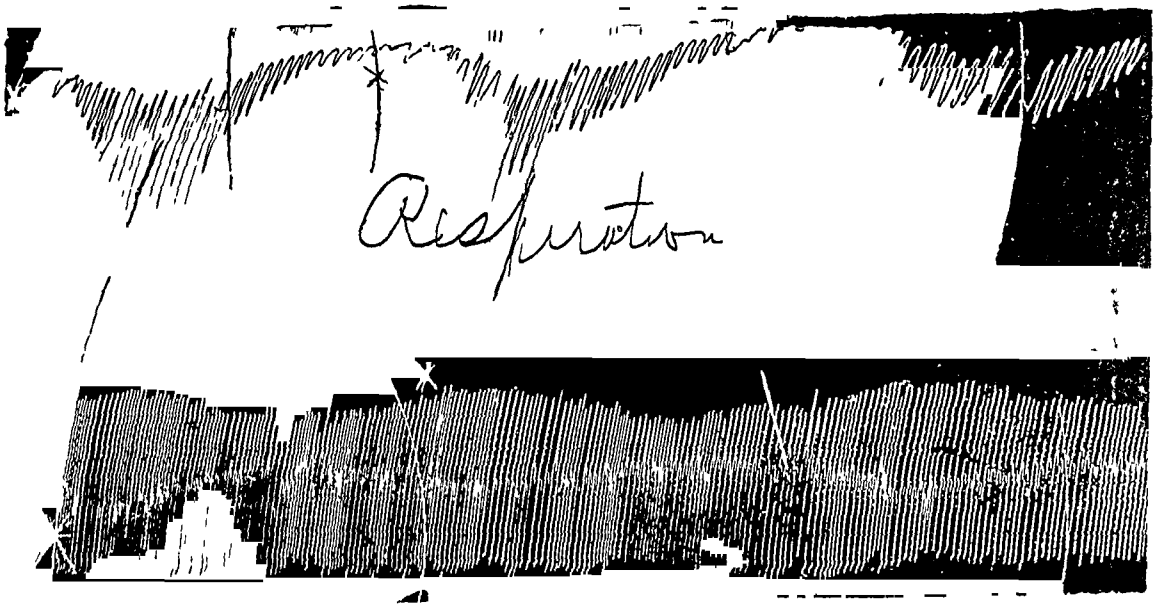

Fig 1 —Tracing showing high blood pressure during apnea in a case of infarct of the lung

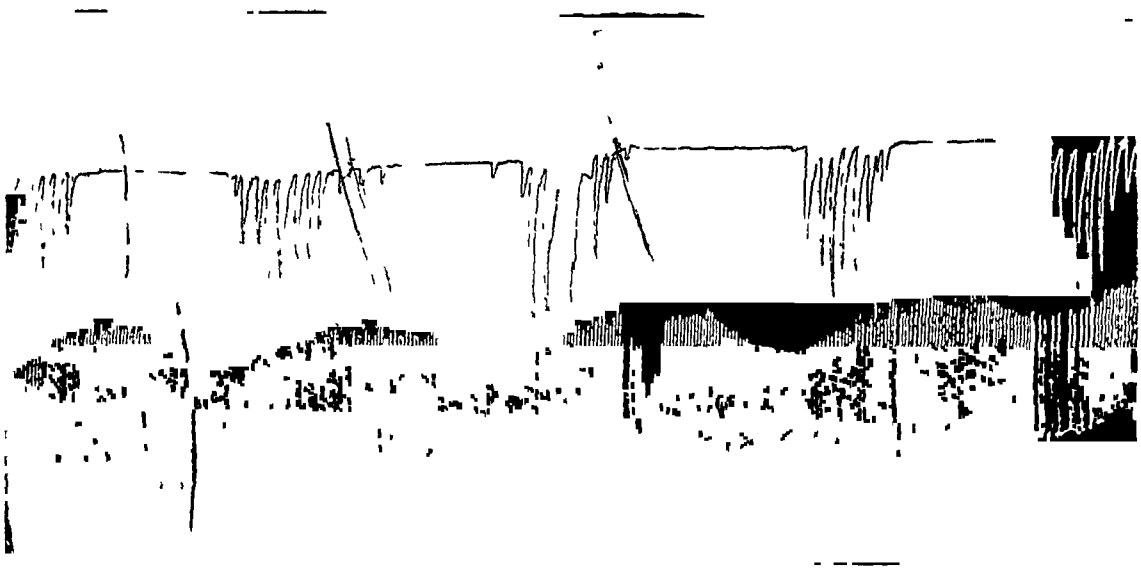

Fig 2 —Tracing showing low blood-pressure during apnea in a case of cerebral hemorrhages

pressure began to fall after the beginning of respiration and rose as respiration diminished

Aside from blood-pressure a few observations are noteworthy The apex-beat showed an increase of amplitude in all cases during the period of hyperpnea The pulse-rate was increased with each rise of blood-

pressure There were numerous extrasystoles in cases of arteriosclerosis during the period of hyperpnea There was more or less irregularity of the pulse in all cases during this period Traube-Hering waves were marked in one case The venous and liver-pulses showed little change throughout the two periods, the auricular waves increased in size and the a-c interval was lengthened during apnea

Case 15 showed pseudohemisystole, a condition in which, in a bigeminal beat of the heart, the second beat of the heart is too weak to propagate an arterial pulse This is of considerable interest, inasmuch as Cohnheim and Welch[3] showed that a paralysis of the left ventricle with the right still beating was a mechanical cause of pulmonary edema

It would seem that the mechanism of the changes of blood-pressure in Cheyne-Stokes respiration associated with increased intracranial tension is as follows The intracranial tension being higher than the general blood-pressure, cerebral anemia exists and apnea is present The vasomotor centers are automatically stimulated to raise the general blood-pressure in an effort to produce an equilibrium between it and the intracranial tension As the general blood-pressure rises respiratory movements recommence at their height the vasomotor centers are no longer stimulated and the general blood-pressure again falls and the respiratory movements diminish and finally cease

3 Cohnheim and Welch Ueber acutes Lungenoedema, Cohnheim's gesammelte Abhandlungen, Berlin, 1885, p 593

THE EFFECT OF PRESSURE-LOWERING DRUGS AND THERAPEUTIC MEASURES ON SYSTOLIC AND DIASTOLIC PRESSURE IN MAN*

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The effect of various vasodilators on the systolic pressure in man has ben carefully studied by several investigators,[1] but changes in diastolic and pulse-pressures accompanying the systolic changes have received but scant attention, diastolic and pulse-pressure being regarded as of theoretical interest only Recent investigations,[2] however, indicate that the pulse-pressure is an important factor in determining the efficiency of the circulation and of more value in prognosis than the systolic pressure To quote from Erlanger and Hooker,[3] "the knowledge of any one of the blood-pressures [systolic, diastolic or mean] throws but little light on the conditions of the circulation"

For this reason, observations on the action of various drugs and therapeutic measures on the pulse-pressure seemed of value since by such means the indications and contra-indications for their use might be more clearly established This paper deals with the effects of various vasodilators and pressure-lowering measures on the systolic, diastolic and pulse-pressures, and on the pulse-rate In a second paper the effect of such changes in the circulation on the excretion of urine will be discussed

The patients chosen for the observations were selected at random from among those entering the hospital showing permanent hypertension All of them showed a continued systolic pressure of 180 or over. Of the twenty patients studied, sixteen were classed as cardiorenal as they showed cardiac hypertrophy and dilatation and some general arterial change as well as evidence of nephritis; two showed marked arterial degeneration with no evidence of renal change beyond that due to vascular change, and

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*From the Henry P Walcott Fellowship in Clinical Medicine, Harvard Medical School

1 Matthews Vasodilators in High Pressure, Quart Jour Med 1909, II, 261 Miller, J L Hypertension and the Value of Various Methods for its Reduction Jour Am Med Assn 1910 liv, 1666 Hewlett, A W Effect of Amyl Nitrite Inhalations on Blood-Pressure in Man, Jour Med Research, 1906, xv, 383 Cook, H W, and Briggs, J B Clinical Observations on Blood-Pressure, Johns Hopkins Hosp Rep 1903, xi 452

2 Erlanger and Hooker. An Experimental Study of Blood-Pressure and Pulse-Pressure in Man, Johns Hopkins Hosp Rep 1904 xii 145 Hooker. Influence of Pulse-Pressure on Renal Function Am Jour Physiol, 1910, xxvii, 24

3 Erlanger and Hooker Johns Hopkins Hosp Rep 1903 xi 150

are therefore classed as arteriosclerosis, and two showed no arteriosclerosis and only slight cardiac hypertrophy and are therefore labelled nephritis All but one were males, as it was early found that they were better subjects than women for the observations

Observations on the effects of the measures studied were not attempted until the patients had been in the hospital long enough to become accustomed to the use of the sphygmomanometer, and to the hospital regimen Excitement may cause marked fluctuation in the pressure, according to Zabel,[4] and twice-daily observations on the pressures of the patients observed showed considerable variations during the first few days of their stay in the hospital During the remainder of their stay they were in a small and quiet ward, and seldom showed marked changes in pressure which could not be explained on a basis other than psychic

Observations were made as far as possible from meal hours The patients were in the prone or semi-prone position The apparatus used was the Faught sphygmomanometer with the 12-centimeter arm-band Successive observations were taken always on the same arm Observations were taken at regular intervals before and after the administration of drugs or beginning of a therapeutic measure, and care was taken to obviate the production of passive congestion of the arm from the successive constrictions by massage or passive motion between readings The systolic pressure was taken at that point at which the pulse first appeared at the wrist after complete obliteration The diastolic pressure was determined by the auscultatory method, which has been shown by many observers[5] to be remarkably accurate The pulse-pressure was thus about 10 mm less than it would have been had the systolic determination been made by the auscultatory method, but it seemed best to use the commoner method of palpation, in order that the results might be comparable to those of others obtained in the same way The pulse-rate was counted for a full minute, in order that differences of four or eight beats might be accurately ascertained, and that the error due to multiplying a fifteen- or thirty-second count might be eliminated

The results of the observations are given in the following charts and tables A brief explanation of these may make clear the points they would bring out Each section of Table 1, except that marked "vasotonin," shows the results of ten observations on patients who reacted to the drug Those patients who showed no change in pressure after admin-

4 Zabel Sudden Changes in Blood-Pressure and Their Causes, Munchen med Wchnschr, 1910, xlv, 2278

5 Fischer Auscultatory Method of Blood-Pressure Measurement Compared to von Recklinghausen's, Deutsch med Wchnschr, 1908, xxxiv, p 1141 Goodman and Howell Clinical Studies in the Auscultatory Method of Determining Blood-Pressure, Univ Penn Med Bull, 1910, xxiii, 469 Lang and Manswetowa Comparison of the von Recklinghausen and Korotkoff Methods of Blood Pressure Estimation, Deutsch Ztschr f klin Med, 1908, xciv, 441

TABLE 1.—THE RESULTS OF TEN OBSERVATIONS ON THE SYSTOLIC AND DIASTOLIC PRESSURE IN PATIENTS WHO REACTED TO PRESSURE-LOWERING DRUGS

	Systolic			Diastolic			Pulse			
	Max	Min	Aver	Max	Min	Aver	Max	Min	Aver	
SODIUM NITRITE										
Beginning fall	30′	5′	15′	30′	5′	12′	75′	5′	20′	Change in rate noted
Maximum reached	80′	5′	35′	90′	10′	35′	20†	6†	13†	Increase in rate
Duration of maximum	75′	10′	37′	120′	10′	43′	40†	4†	15†	Decrease in rate
Normal regained	180′	40′	135′	180′	10′	88′	180′	40′	92′	Normal regained
Maximum fall	50*	5*	23*	20*	5*	11*				
ERYTHROL										
Beginning change	25′	5′	12′	25′	5′	12′	30′	5′	16′	Change in rate noted
Maximum reached	115′	20′	80′	115′	20′	75′	4†	0†	4†	Increase
Duration of maximum	40′	10′	37′	40′	10′	37′	8†	0†	8†	Decrease
Normal regained	270′	20′	176′	270′	20′	192′	125′	15′	158′	Normal regained
Maximum change	50*	20*	26*	20*	8*	12*				
MANNITOL										
Beginning fall	30′	8′	17′	30′	8′	17′	110′	15′	23′	Change in rate noted
Maximum reached	145′	30′	82′	145′	40′	79′	12†	0†	6†	Increase in rate
Duration of maximum	60′	20′	51′	60′	40′	55′	4†	4†	4†	Decrease in rate
Normal regained	300′	20′	192′	300′	20′	192′	300′	20′	165′	Normal regained
Maximum fall	50*	15*	34*	20*	10*	12*				
VASOTONIN										
Beginning rise	25′	5′	16′	50′	5′	21′	20′	5′	11′	Change in rate noted
Maximum reached	150′	20′	68′	90′	5′	39′	12†	0†	8†	Increase
Duration of maximum	20′	5′	10′	85′	15′	65′	4†	0†	4†	Decrease
Normal regained	420′	120′	222′	420′	120′	218′	240′	120′	181′	Normal regained
Maximum change	70*	15*	30*	30*	5*	16*				
VENESECTION										
Beginning fall	15′	15′	15′	15′	15′	15′	0′	10′	10′	Change in rate noted
Maximum reached	7°	75′	7°	75′	15′	30′	0	0	0	Increase in rate
Duration of maximum	?	?	?	17°+	?	?	16†	0†	9†	Decrease in rate
Normal regained	?	180′	?	?	180′	?	?	170′	?	Normal regained
Maximum fall	30*	10*	23*	20*	20*	12*				

*Mm. †Beats.

istration of the drug are not included in these tables, the purpose of which is to compare the curves produced by the drugs Cases in which the patients did not respond are therefore omitted in order not to distort the curve They will, however, be briefly discussed later The drugs compared are sodium nitrite, erythrol tetranitrate, mannitol hexanitrate and vasotonin The results of venesection, hot-air baths, electric-light baths and treatment with high-frequency currents are likewise tabulated

The effects of amyl nitrite and nitroglycerin are not tabulated here, as they are too transient to admit of accurate study by the method used A curve constructed from the readings obtained after their use, however, indicates that the changes produced are similar in character to those caused by other members of the nitrite group, though less intense and less enduring Careful study of the action of amyl nitrite and nitroglycerin has been made by Hewlett[1] and Matthews[1]

TABLE 2.—INFLUENCE OF PRESSURE-LOWERING THERAPEUTIC MEASURES ON SYSTOLIC AND DIASTOLIC PRESSURE

	No of Cases Showing Fall	No of Cases Showing no Change	No of Cases Showing Rise
High-frequency Currents— 10 cases	1, systolic, 20 mm , diastolic, 0 mm	8	1, systolic, 10 mm diastolic, 10 mm
Hot air baths— 10 cases	4, average systolic, 24 mm diastolic, 12 mm	5	1, systolic, 10 mm diastolic, 10 mm
Electric light baths— 10 cases	5, average systolic, 18 mm diastolic, 10 mm	4	1, systolic, 10 mm diastolic, 10 mm

Comparing the tables on sodium nitrite, erythrol and mannitol, it will be seen that there is considerable variation in the rapidity, intensity and duration of their actions They all show the same maximum fall, systolic and diastolic, but the average systolic fall caused by mannitol is greater than that brought about by the other two while the average diastolic fall is practically the same for all Mannitol, therefore, diminishes the pulse-pressure more markedly than the other two This is shown graphically in Chart 1, in which the average effect of each drug, based on ten observations each, is shown The tables likewise show that sodium nitrite has a more marked effect on the pulse-rate than the other two drugs, in this respect acting much like nitroglycerin and amyl nitrite The drugs whose effect lasts longest appear to cause less disturbance of pulse-rate and less change in diastolic pressure than the quicker acting members of the group The reason for this probably lies in the chemical composition of the drugs, mannitol and erythrol bring hexa- and tetra-nitrates, from which the nitrites are more slowly absorbed than from sodium nitrite or nitroglycerin

In spite of the individual differences, however, the effect of all the members of this group on the circulation is essentially the same The type action as shown by Chart 1 is as follows Systolic pressure is lowered,

diastolic pressure is lowered, the fall bearing to the systolic fall a strikingly constant ratio of approximately 1 to 2 Thus pulse-pressure is diminished The ratio of pulse-pressure to systolic pressure, however, approaches normal more nearly than under the conditions of hypertension This can be seen in Charts 2, 3 and 4, in a curve typical of the drug

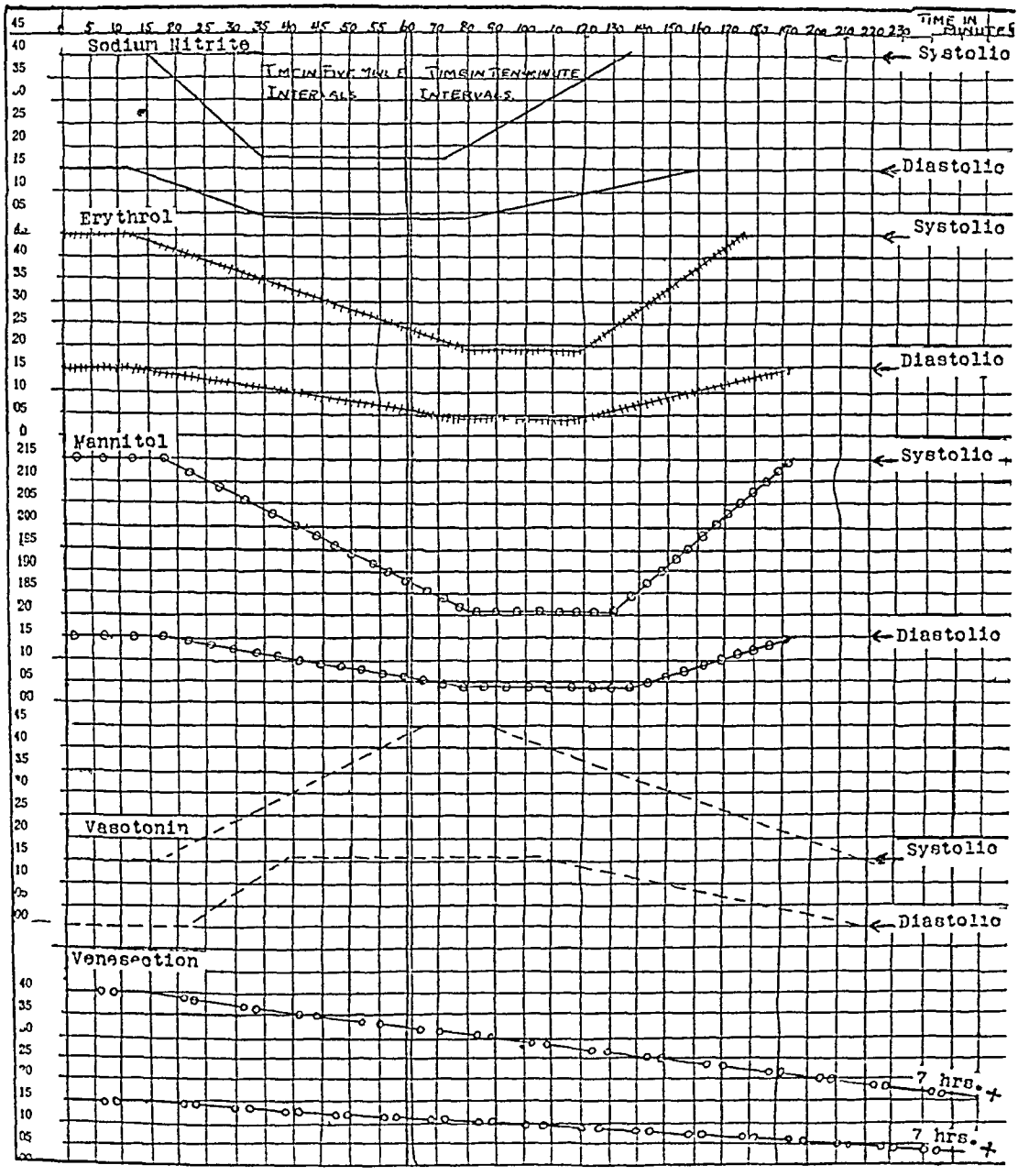

Chart 1—The relative effects of the various measures studied on systolic, diastolic and pulse-pressure The three upper curves are constructed from ten observations each, the two lower from five observations each The lower of each pair of lines represents the diastolic pressure

used These charts likewise show that the pulse is as a rule accelerated

To this typical action there are several exceptions The commonest is absence of any action at all This occurred in three cases with sodium

nitrite, and in six with erythrol With the latter drug the preparation was probably at fault in three cases, it being the same as that with which Matthews[1] reported negative results in his article In the other three cases, and in the two in which sodium nitrite failed to act, there appeared to be no common feature One reacted later to the same preparation, one had already shown a fall in pressure after the administration of erythrol The presence or absence of edema did not play an important part in influencing the action of the drug, for three of the cases which gave no fall showed no edema, while in six cases showing marked edema

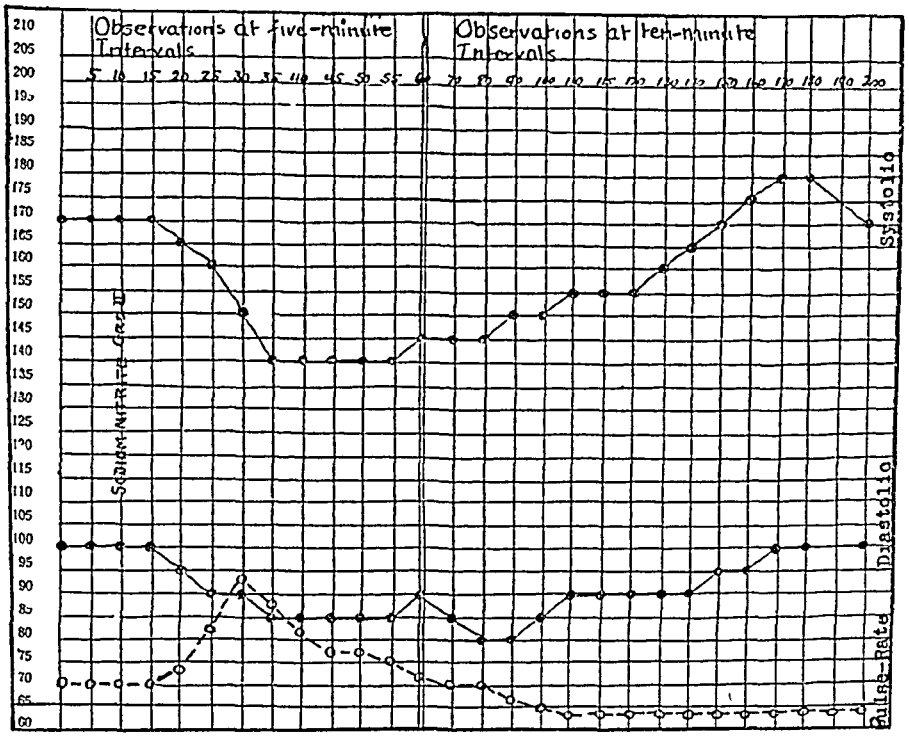

Chart 2.—A curve obtained by the use of sodium nitrite The acceleration of the pulse-rate during the fall in pressure is the rule, slowing of the pulse at that point was observed in a few cases The systolic rise above the original level at the end of the curve is more common with this drug than with those causing a more gradual curve No terminal diastolic rise above the original level was noted Diastolic fall half the systolic

of the lower extremities the patients reacted promptly and typically to a vasodilator Another exception to the typical action of the group is a rise in pressure following the administration of the drug This occurred but twice in this series of observations Systolic and diastolic pressures were both affected, the normal curve being simply inverted

The pulse-rate is usually quickened but may be slowed The former action is the more common, and the latter must be regarded as the exceptional result The cases in which it occurred failed to show any common feature which might be advanced as an explanation of the action

Theoretically it should be possible to maintain the blood-pressure at a permanently lower level by the frequent administration of any one of the drugs under discussion In the twenty cases in which observations were made this was impossible for more than forty-eight hours If the administration of the drug were then continued, the patient developed, as a rule, headache, restlessness and in some cases dyspnea, even though the pressure was at its original level The symptoms therefore can be fairly attributed to the drug, though the blood showed no evidences of methemoglobin in any case Omission of the drug for a few days would be followed by a reappearance of its characteristic action when it was once more resumed

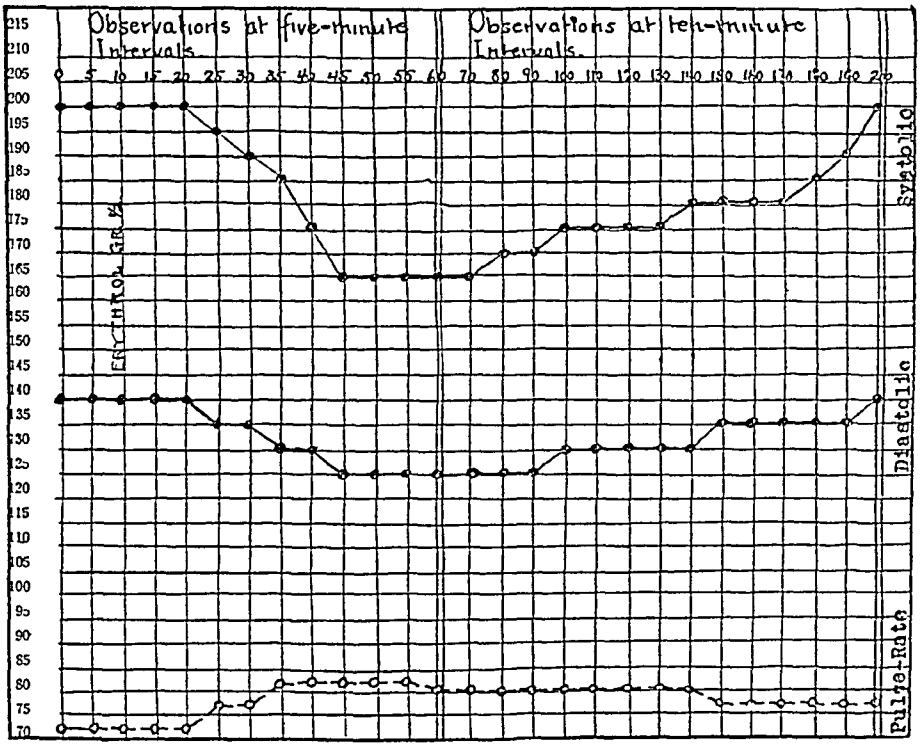

Chart 3 —Curve characteristic of the action of erythrol Less acceleration of pulse than with sodium nitrite Diastolic fall very slightly—less than half systolic

Several authors in Germany[6] reported satisfactory results from the use of vasotonin (a preparation of yohimbin and urethan), its action being reported as more permanent than that of the nitrites The curve in Chart 1 showing its effect is constructed from observations in five cases, in all of which its administration was followed by a rise of systolic and diastolic pressure Chart 5 shows a typical curve obtained from an arteriosclerotic patient In one case its administration was followed by a severe anginal attack accompanying the rise in pressure, in another there was marked vertigo

6 Muller and Fellner Deutsch med Wchnschr, 1910, xlv, 914, and 961 Fellner Klin Wchnschr 1910 xxi, 993

It is remarkable that even so small a series as five cases should without exception show a rise in pressure following the use of the drug Each patient reacted in a perfectly typical manner to the nitrites both before and after the administration of vasotonin The number of cases is too small to furnish conclusive evidence against the preparation but large enough to establish the fact that its action is uncertain, and that it is unsafe to administer it in cases showing marked hypertension

Of the other measures for lowering high tension which were studied, venesection gave the most interesting results Chart 1 shows the duration of action compiled from five curves as compared with the duration of the drug method of reducing blood-pressure Its action is much more pro-

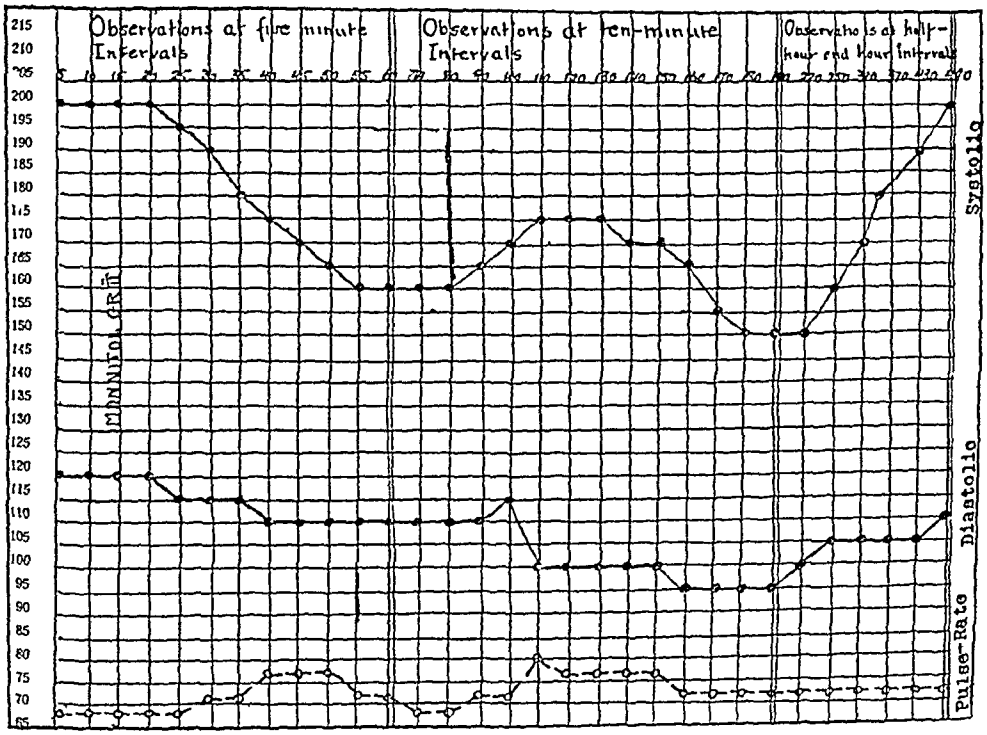

Chart 4.—Effect of mannitol Acceleration of pulse slight Diastolic fall slower than systolic and but slightly more than half as great Diastolic rise slower than systolic, resulting in increased pulse-pressure at end of curve

longed than that of any drug studied In four of the five cases observed, pressure did not regain its original level in twelve hours In one case the pressure remained reduced for thirty-six hours

Chart 5 shows a single curve after venesection It was the second one performed on the patient, who was moribund with uremic symptoms, and both the extent and duration of the fall obtained are less than in the other cases For this very reason, however, it admits of more complete analysis and is therefore selected for reproduction

It will be seen that the diastolic pressure fell just half as far as the systolic, a ratio already noted The maximum diastolic fall, however,

was more prolonged than the systolic, so that an increased pulse-pressure with a lowered diastolic pressure was the result Such a condition means a nearer approximation to the normal "coefficient of pressure" [7] than obtained before the venesection

The results of electric-light and hot-air baths, and of treatment with high-frequency currents were necessarily studied in less detail, since any attempt to record pressures during such treatments would have seriously

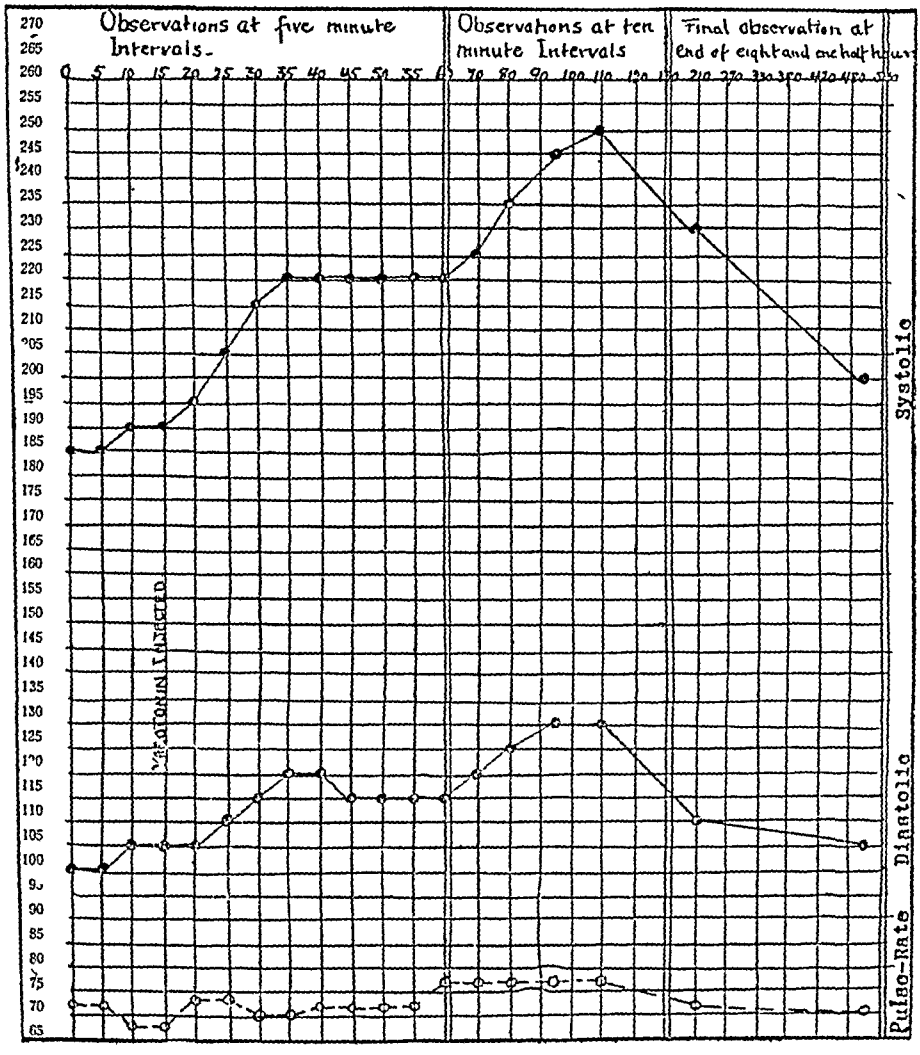

Chart 5.—Effect of vasotonin A considerable and prolonged rise in both systolic and diastolic pressure Pulse practically unaffected The patient was suffering from arteriosclerosis His kidneys were apparently only slightly affected

interfered with their efficiency Reference to the table shows, however, that a fall in pressure was more frequent with electric-light or hot-air baths than with high frequency treatment,[8] which indeed gave discour-

7 Gibson, G A Arterial Pressure, Edinburgh Med Jour, 1911, New Series v-vi, 1907

8 Saylor, Ettie Effects of Electrical Treatment on High Blood-Pressure, Brit Med Jour, 1910, ii, 1052

aging results The average systolic fall obtained with the other methods was about 20 mm , the diastolic half of that Pressure usually returned to the original height in an hour or less The pulse was always accelerated during the treatment but reached normal soon after its termination

The number of cases showing no change in pressure is about equal to those in which a fall was recorded As in the case of the vasodilators, no common symptoms could be assigned to such cases The patients did not, however, "react" well to the baths, perspiration being very slight, and relief after the bath was absent The patients who "reacted well," i e , perspired freely and felt relieved after the bath, all showed lowered pressure

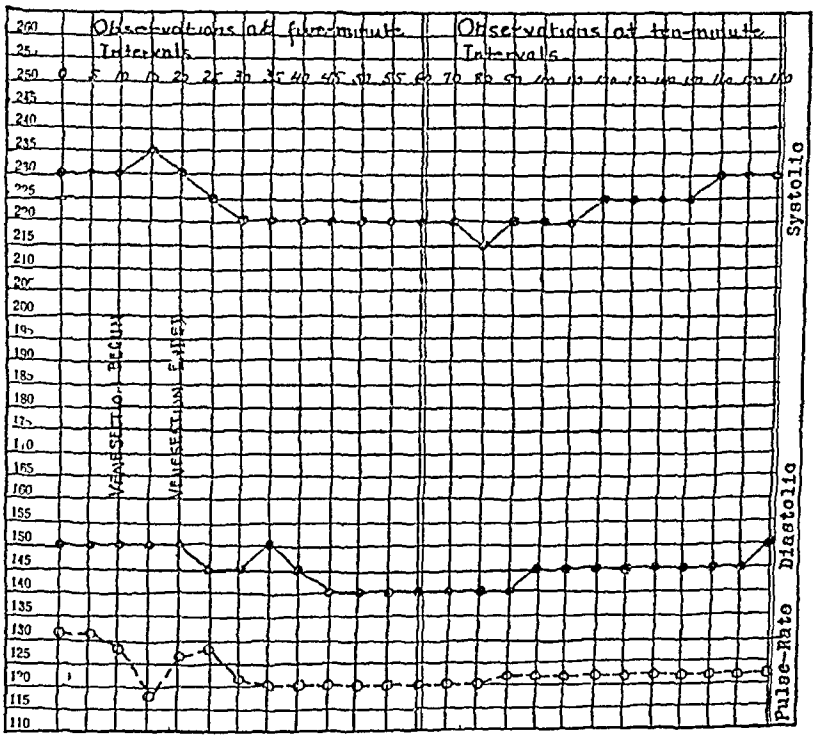

Chart 6 —Effect of venesection Action in this case less marked and less sustained than in others Patient uremic and moribund Pulse slowed Diastolic fall two-thirds as great as systolic, therefore pulse-pressure diminished less than by vasodilators

CONCLUSIONS

1 The reduction of systolic pressure in cases of hypertension by the use of nitrites, venesection, electricity or hot air, is accompanied by a fall in diastolic pressure amounting, as a rule, to approximately one-half the systolic fall

2 Such a reduction produces a coefficient of pressure more nearly approaching the normal than does the coefficient under the conditions of hypertension

3 Sodium nitrite reduces diastolic pressure more rapidly than the more complex compounds, thus causing a shorter initial diminution of pulse-pressure than is obtained with mannitol or erythrol Its effect on the pulse is more marked than that of the other two drugs The duration of its action is slightly less

4 None of the nitrite group is efficient for maintaining a pressure at a permanently lowered level, as a tolerance is soon acquired and increasing the dose is apt to cause unpleasant symptoms

5 Venesection has a more lasting effect in lowering the pressure than have any of the drugs considered in this paper The diastolic pressure is depressed longer than the systolic, the pulse pressure thus being increased

6 The effect of hot-air baths, electric-light baths and treatment with high-frequency currents is uncertain A fall in pressure, if produced, is transient

7 Vasotonin is not certain in its action and is not safe to use in cases showing marked hypertension, an increase of which might bring about untoward results

8 In cases with permanent hypertension the effect on renal function of lowering the general pressure is an important and interesting point which will be discussed in a later paper

I wish to thank Dr F C Shattuck for making this work possible, and for interest and encouragement at all times My thanks are also due to all the members of the visiting staff and to all connected with the Massachusetts General Hospital who have aided me so kindly

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THE CAUSE OF MALARIAL ANEMIA, AND THE INTRAVASCULAR MIGRATIONS OF THE MALARIAL PARASITE*

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All investigators agree that in few conditions does so marked and rapid anemia develop as in malaria. The rapidity of its development, as well as its severity, has often excited notice For example, Dionisi[1] noted a reduction of 500,000 red corpuscles in twelve hours, and also demonstrated that there is no intimate relation between the number of parasites present in the peripheral blood and the destruction of red corpuscles during a paroxysm Grawitz[2] noted a loss of 4,000,000 red corpuscles in six days Kelsch[3] found a diminution of red corpuscles during intervals between paroxysms, with an especially great decrease in cases of acute malarial infections, one case showing 500,000 to the cubic millimeter Marchiafava and Bignami[4] found that there was a destruction of red corpuscles in non-febrile cases of larval malaria, and Ewing[5] found post-febrile anemia to be the rule in all very severe cases of malaria Manson[6] writes

> We find a decided oligocythemia greatly in excess of anything we might expect, or which can be accounted for by, or is in correspondence with, the proportion of corpuscles attacked or directly consumed by the parasite, judging from what we see in the peripheral blood What are the clinical facts? One or two paroxysms only of some malarial fevers may be immediately followed by an anemia so pronounced as to be discernible to the eye in the intense pallor of the skin and visible mucous surfaces On counting the corpuscles in such a case we note a regular drop in their number of from 5 to 10 per cent per paroxysm Often after a single paroxysm of some pernicious fever as many as half a million, or even one million, corpuscles per cubic millimeter drop out of the normal five million, and this reduction may go on, as paroxysm follows paroxysm, until the corpuscular richness has fallen to one million, or even less Not only is there this marked diminution in the proportion of the corpuscles to the bulk of the blood and in their hemoglobin value, but there is, furthermore, in all malarial conditions of any considerable standing, a marked diminution in the volume of blood Thus it comes that at the post-mortem examination of such a case we do not encounter that congestion of the organs which is so usual a feature in most

* Work done under a grant from the American Medical Association, Committee on Scientific Research

1 Dionisi Lo Sperimentale, 1891, F III and IV, 284

2 Grawitz Quoted from Cabot Clinical Examination of the Blood, Ed 5, p 451

3 Kelsch Arch de physiol norm et path, 1875, second series, II, 690

4 Marchiafava and Bignami Deutsch med Wchnschr, 1892, XVIII, 157

5 Ewing Clinical Pathology of the Blood, 1903, p 460

6 Manson Tropical Diseases, 1903, pp 94 and 95

specific fevers On the contrary, although in quite recent cases visceral congestion may be marked enough, if a malarial fever has been of any considerable duration, the venous system, with the exception of that appertaining to the spleen, liver and portal system generally, may be markedly empty

This anemia of malarial fevers has never been satisfactorily accounted for It has been generally believed that each malarial parasite grew up and finished its life cycle within a single corpuscle, the segmentation of the parasite corresponding usually with the final destruction of the corpuscle But when we consider that, in some cases, the degree and rapid advance of the anemia seem to be out of all proportion to the number of parasites present, some supplementary hypothesis has to be invoked — some other factor presupposed

In malarial hemoglobinuria, in which an enormous destruction of red corpuscles occurs, it is usually assumed that this supplementary factor is the quinin ingested for therapeutic purposes Other elements have been considered to play a part Thayer,[7] in discussing this problem, is led to consider that "the destruction is probably too great to be dependent wholly on the disintegration of parasitiferous elements We are compelled to suppose the existence of some condition which renders the uninfected red corpuscle unusually vulnerable, possibly some change in the blood-serum by which its isotonicity is markedly disturbed"

Manson,[8] in discussing the same problem, writes

> May it not be that at a particular stage in all malarial fevers which corresponds to the breaking down of the sporulating parasite, there is a sudden liberation of some hemoglobin-dissolving substance that this substance is set free in the circulation, and that being there, retaining its digestive properties, it continues to act as a hemoglobin solvent, and so dissolves out a proportion of the hemoglobin from the otherwise healthy corpuscles?

Ewing[9] supposes that "the postcritical anemia is principally referable to the globucidal action of the serum, dependent on the presence of a malarial toxin Some of the facts [leading to this belief] are the disproportion between the anemia and the number of parasites present, and the steady diminution in the loss of cells in the second and third as compared with the first paroxysm"

But in most discussions of this kind it is taken for granted that each parasite finishes its life-cycle within a single corpuscle It is true that some observers have recognized another possibility Thus, Thayer[10] has confirmed Bastianelli and Bignami[11] in their observation that a half-grown parasite may abandon its corpuscle

> Occasionally, pigmented bodies may be found outside the red corpuscles free in the plasma Some of these represent entirely full-grown bodies which have

7 Thayer Lectures on Malarial Fevers, 1897
8 Manson Tropical Diseases, 903, p 103
9 Ewing Clinical Pathology of the Blood, 1903 p 461
10 Thayer The Malarial Fevers of Baltimore, 1895 p 81
11 Bastianelli and Bignami Quoted from Thayer (See 10)

destroyed the surrounding corpuscle, while in other instances the half-grown forms may actually leave their host This process may be occasionally observed under the microscope The corpuscle containing the parasite suddenly collapses, like a bladder, its color becoming immediately diffused into the surrounding plasma, while the parasite, at the same moment, bursts out of the corpuscle into the serum Almost immediately after its escape from its host, the free parasite becomes irregular in outline or fragmented (Plate II, Fig 6) The pale, decolorized, expanded shell of the corpuscle may sometimes be distinguished for a short time after the escape of the parasite

The abandonment of corpuscles by parasites in various stages of development has been observed by Dock[12]

"They seem to have a special tendency to escape from the blood-corpuscles at early periods" He figures eight changes of form in "a small, free, hyaline body" (observation lasting five minutes, the parasite observed was pigmented, which proved that it had previously been attached to a corpuscle), and again "The plasmodium may escape from the corpuscle at any stage and, at any time, either in the corpuscle or free in the plasma, can undergo segmentation"

DaCosta[13] states that "some parasites escape prematurely from the erythrocyte at an early period of their life history" And Laveran[14] refers several times to parasites free in the blood-serum In discussing the relation of the parasite to the corpuscle, Laveran says "The probability is that they simply adhere to the blood-corpuscles by pressing on them What makes this supposition more likely to be true is that the parasitic elements are often found in the blood in a free state and that at all periods of their development" And again, he describes "small elements which scarcely measure the sixth part of the diameter of one blood-corpuscle, and which only enclose one or two granules of pigment These bodies are sometimes isolated, sometimes grouped together in threes and fours, now free in the blood now adherent to blood-corpuscles" Again, he describes "small transparent elements, the smallest of which only measured 1 micron in diameter and only contained one or two granules of pigment These bodies are sometimes free, sometimes adherent to red blood-corpuscles" And Mannaberg,[15] in referring to free parasites, says

> The spores, which have become free, are often demonstrated in enormous numbers The way in which their structure takes on stain is so striking that one is prevented from suspecting them to be "degeneration forms"
>
> The ameboid bodies, too, which are often developed further than their spore forming stage, are not infrequently to be found free in the liquor sanguinis fully retaining their structure

These observations regarding the behavior of the malarial parasite in moist preparations outside the body have been repeatedly confirmed The

12 Dock Studies in the Etiology of Malarial Infection, Med News, 1890, lvii, 59, and Further Studies in Malarial Disease, Med News, 1891, lviii, 602

13 Da Costa Clinical Hematology, 1901, p 365

14 Laveran Paludism, 1893, pp 11, 12 and 13

15 Mannaberg The Malarial Parasite, 1894, pp 277 and 278

fragmentation of parasites under the artificial conditions of being placed *in vitro* between slide and cover preparations, above referred to, apparently does not occur within the circulating blood At any rate, I have been unable to find any such appearances in stained specimens The behavior of the parasite outside the body may be explained in a number of ways Possibly the pressure of the cover-glass, or the atmospheric changes consequent on the gradual drying up of the smear, may so affect the parasite that it is unable to attack another corpuscle after it has destroyed the one it was attached to Possibly the chemistry of the serum or the osmotic conditions occurring in the necessarily abnormal slide-and-cover preparation, make it impossible for the parasite and the corpuscle to react to one another in the ordinary way

Various explanations have been given to account for the presence of young pigmented parasites free in the blood-serum Dock[12] considered that they were either "varieties of the forms which carry on the typical process in malaria" or that they "have an independent existence," and as to their origin he says "My observations show beyond doubt that they are derived from certain endoglobular forms" Many observers consider the free pigmented parasites as evidence of parasitic senility or degeneration Had these free parasites been recognized as migrating parasites capable of destroying more than one corpuscle, the cause of the anemia of malarial fevers would, I think, have been obvious

In contradistinction, then, to all previous writers known to me, my studies have led me to believe that the cause of the rapid and serious anemia of malaria is the destruction of corpuscle after corpuscle by migrating parasites

EVIDENCE OF THE MIGRATION OF MALARIAL PARASITES

That a malarial parasite may destroy more than one corpuscle is strongly suggested by the following facts which I will present in advance as a summary of my findings

1 I find in the blood-serum many free, pigmented and apparently healthy malarial parasites The great majority of these free parasites have a compact structure and show no evidence of ameboid activity

2 In the same smear, attached to apparently healthy and therefore newly invaded red corpuscles, I find pigmented parasites whose stages of development are the same as those seen in parasites free from corpuscles Their pigment seems to mean the residuum of another corpuscle previously attacked

3 Attached to disintegrating red corpuscles, I find apparently healthy pigmented parasites in stages of development corresponding to those of the "free parasites" and "parasites on healthy corpuscles" mentioned in the last two paragraphs

4 In the same smear I find corpuscular remnants free from parasites but occasionally showing traces of pigment which I believe are characteristic of the recent presence of parasites

All these four sets of phenomena may be seen in the same smear, or on the other hand, only one or two of these stages may be represented in a smear

I interpret these four sets of facts as representing the stages of a parasitic migration Thus we have

1 Parasites free in the serum but containing pigment and therefore previously attached to a corpuscle These I believe are in migration

2 Parasites which I believe have recently attached themselves to corpuscles I say "recently" because, from the staining reactions and other appearances of the corpuscles, I believe them to be still healthy and not seriously damaged by the parasites

3 Parasites attached to degenerated corpuscles which, presumably, are degenerated because the parasite has been at work there for a longer period

4 Corpuscles deserted by the parasite but still showing evidence of its previous presence

Each of these four stages will now be discussed more in detail

THE SIGNIFICANCE OF THE PRESENCE IN THE BLOOD-SERUM OF MANY FREE, APPARENTLY HEALTHY, PIGMENTED PARASITES

The fact that many of the smears which I have examined contained free parasites in certain definite stages of development, while parasites in other stages of development, in the same smear, are invariably found attached to corpuscles, seems to me to exclude the idea that in the technic of spreading the smears the parasites have been pushed away from their corpuscles For if the technic of spreading the smears had forced the parasites loose, there would be no such limitation and uniformity in the stages of development exemplified in the free parasites Thus in Case 1 (Plates I, II and III, double tertian infection), there were parasites in five stages of development found free (Plate III) in one smear (omitting the parasites resulting from immediate segmentation, Plate III, Figs 1 and 21a) But in this smear, while there were many presegmenting parasites seen attached to corpuscles, there were no presegmenting parasites found free, and only one found on a degenerated corpuscle, and as this corpuscle was also occupied by two young parasites (Plate II, Fig 3), the presegmenting parasite was probably not alone responsible for the degenerated condition of the corpuscle On the other hand, I found in the same smear *two* presegmenting parasites attached to an apparently healthy corpuscle (Plate II, Fig 4)

Again, in a smear from Case 2 (Plates IV and V) only presegmenting parasites and a few segmenting bodies were seen entirely free from the corpuscle, while, on the other hand, all the half-grown parasites and all the small ring-forms in the same smear were attached to corpuscles

In Case 3 (Plate V) parasites in several stages of development were seen, but only those in three stages of development — namely half-grown, presegmenting and segmenting — were found free from corpuscles In Case 4 (Plate VI) parasites in five stages of development were found free from corpuscles while parasites in other stages of development were found attached to corpuscles

Surely we cannot explain this uniformity in the ages of the parasites found free in single smears as a result of the technic in spreading the smears nor can it be explained as resulting from the action of quinin for quinin had not been given in these cases before the smears were taken What can the above facts mean except that at certain stages of their growth the parasites, though still healthy, leave the corpuscle?

Dock[12] says, in regard to the uniformity of the number of free parasites in the blood "As regards numbers free pigmented bodies seem to vary more in different cases, than in the same case at different times"

The pigmentation of the parasites found free in the blood-serum is evidence of their previous attachments to, and conquests of corpuscles from the hemoglobin of which the pigment is derived I have often noticed that very young parasites attached to moribund corpuscles may contain but a small amount of pigment Apparently a parasite can destroy a corpuscle and yet derive but a small amount of pigment from it This suggests that we might form a rough estimate as to the number of the previous attachments of the parasite to corpuscles by noting the amount of pigment which the parasite contains All observers have noted that the larger the parasite becomes the more pigment it contains

THE PARASITE JUST LANDED

Parasites in stages of development corresponding to those found free in the blood-serum were always found in the same smear attached to red corpuscles showing all the appearances of health (Plate I Figs 2 and 3 Plate II Fig 4 Plate IV Figs 13 and 15 Plate VI Fig 4) The suggestion is that these parasites have "just landed" from their last migration have attached themselves to the substance of a fresh corpuscle and have not as yet had time to do any considerable damage there This observation of parasites on healthy corpuscles is quite in accord with that of Da Costa[16] who says that 'simple decoloration of the erythrocyte appears to follow no fixed rule for segmenting bodies have been observed

16 Da Costa Clinical Hematology 1901, p 373

both in perfectly hyaline [i e, moribund] and in apparently healthy corpuscles" If my hypothesis of migration is correct, this apparent capriciousness is easily explained

Another bit of evidence pointing in the same direction is illustrated in Plate II, Figure 4, in which we see that the color-index of a corpuscle to which two presegmenting parasites have attached themselves is practically the same as that of another corpuscle to which a young, pigmented parasite has just (as I believe) attached itself (Plate I, Fig 2) If one parasite grew up and died on a single corpuscle, the hemoglobin of this doubly infected red corpuscle ought to be practically gone, but, in fact, it shows as high a color-index as the corpuscle just captured by the young parasite Therefore, in my belief, the corpuscle illustrated in Plate II, Figure 4, has just been invaded by two old parasites which are "on the move"

THE PARASITE "WELL-SETTLED"

In Case 1 (Plates I, II and III) we see (1) many healthy-looking, pigmented parasites attached to disintegrated corpuscular remains These parasites are in the same stages of development as (2) other parasites seen free, and (3) parasites seen on healthy corpuscles in the same smear (In Plate I, Figure 12, two young pigmented parasites are seen on a disintegrated corpuscle, while another parasite in the same stage of development is seen to be on a healthy corpuscle) These facts I take to be evidence of the successive stages in the life history of the parasite In the first (1), it is almost ready to leave on its voyage of migration, in the second (2), it is on the voyage, and in the third (3), it is "just landed" The exceptions to this plan of development occur in instances of multiple infection of a corpuscle (Plate II, Figs 3 and 6) When multiple infection occurs, some of the parasites may be set free while others have not reached the stage of development at which they would have been able, unaided, to destroy the corpuscle (Plate III, Fig 16)

The dying red corpuscles to which parasites, prior to the actual segmenting stage, are attached, are greatly expanded, this expansion is probably due to a loss of corpuscular substance with subsequent flattening produced by the pressure exerted in the technic of spreading the smear These degenerated corpuscles show, in the majority of cases, little resemblance to the corpuscular remnants commonly seen in connection with segmenting parasites (Plate II, Fig 7) As a rule they differ from them in staining reaction as well as in size Possibly the difference in size is due to the fact that when an old parasite, nearly ready to segment, attaches itself to a fresh corpuscle and has but a short time to stay there, it does not exploit and destroy the corpuscle to anything like the same extent that we see when a younger parasite attacks a corpuscle

Many of the moribund corpuscles to which parasites are still attached show a peculiarly uniform shape (Plate II, Figs 1 and 5, and Plate III, Fig 11) The corpuscle becomes enormously distended and resembles a granular disk with a narrow crescentic band occupying a portion of the periphery This crescentic band is shown by fine focussing to represent a thickening, as well as a widening, of the corpuscular substance and extends about half way around the circumference of the corpuscle [17] This form of degenerated corpuscle may be schematized thus

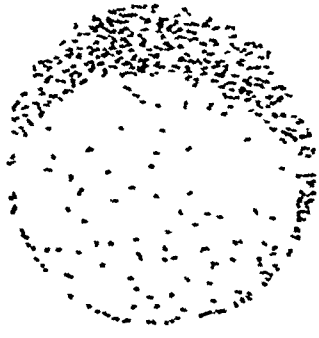

Diagram of degenerated corpuscle

The staining reaction of these corpuscles, with Wright's modification of Leishman's stain, is a delicate pink color The granulations take a more delicate stain than do Schuffner's dots The granules to which I refer apparently do not increase in size with the size of the corpuscle or with the age of the parasite Maurer[19] states "Schuffner's dots grow with the enlargement of the blood-corpuscle (i e, with that of the parasite), not in number, but in bulk"

(Compare, in Plate II, Figures 1 and 5, the granules of the degenerated corpuscles, with Schuffner's granulations in a red corpuscle containing two tertian parasites [Plate II, Fig 9] and note how much more distinct Schuffner's granules are Schuffner's dots are stained pink on the yellow background of the red corpuscle, while the granular degenerated corpuscles are stained pink *in toto*)

CORPUSCULAR REMAINS DESERTED BY THE PARASITE

In smears of malaria we often find enormous numbers of what I believe to be the remnants of used-up corpuscles free from parasites (Plate II Figs 8 to 10 and Plate VII Fig 16) I believe that this indicates that after practically destroying a corpuscle the parasite has

17 Did Mannaberg[18] describe this appearance of the degenerated corpuscle with the parasite attached when he wrote "small deeply pigmented parasites are sometimes seen lying as it were in a folded veil which is formed of shrivelled and completely decolorized blood corpuscles"?

18 Mannaberg The Malarial Parasite 1894 p 278

19 Maurer Quoted from Loffler (malaria) in Modern Clinical Medicine 1910

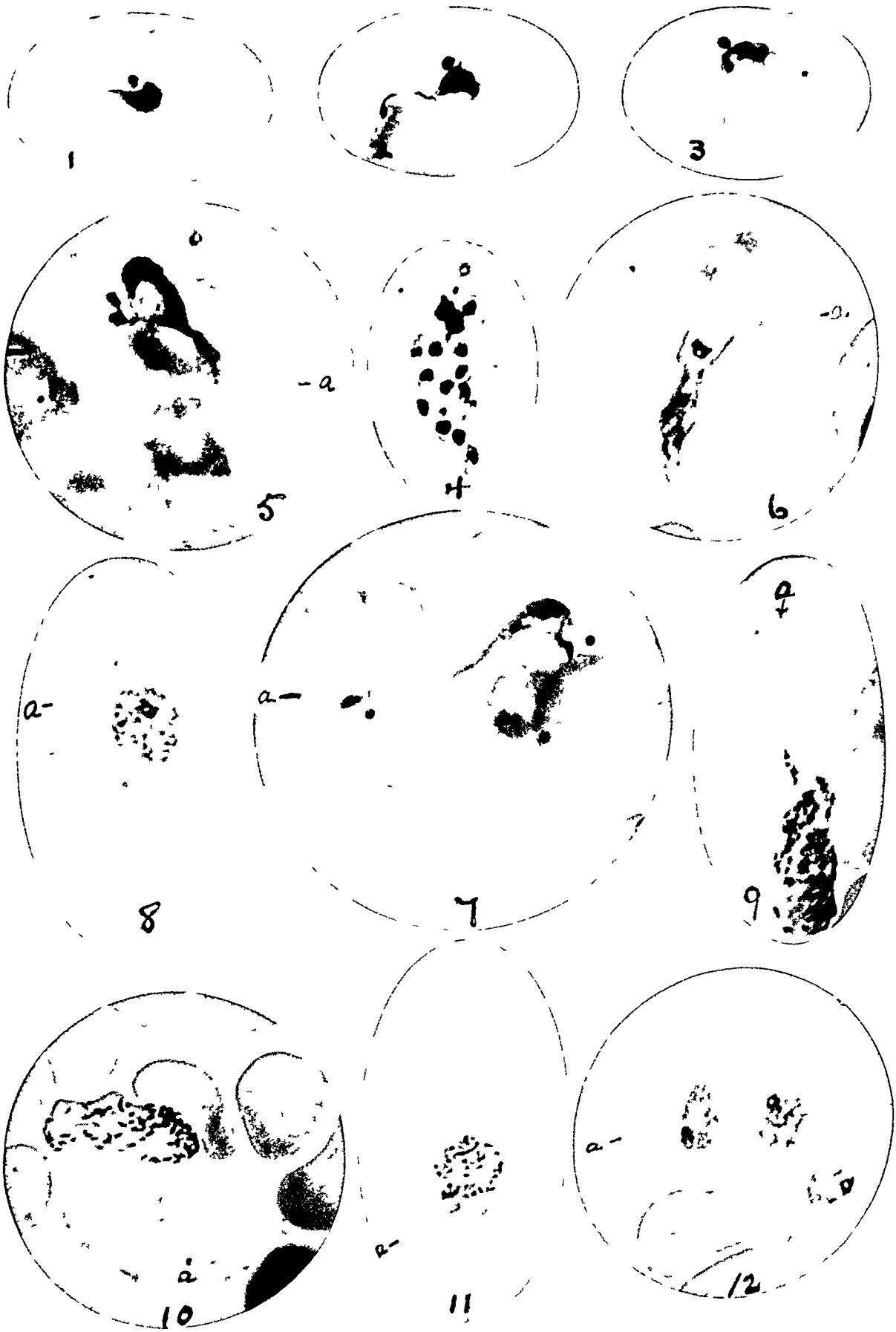

PLATE I

Plate I—Migration of malarial parasites

Case 1—Tertian malaria (double infection) While I have evidence of migration in the quartan and estivo-autumnal infections as well as in tertian infections, I have confined my illustrations for this paper to the tertian parasite Figures from 1 to 6 and from 8 to 12, magnification is × 1850 figure 7, magnification × 1600 Stained by Wright's modification of Leishman's stain

Figure 1—A young tertian parasite, pigmented, free in the blood serum showing the thread-like appendage of cell-protoplasm which the parasite seems to require for attachment to the surface of the red corpuscle The pigmentation of this young parasite proves that it has previously invaded a red corpuscle (see Plate VII, Fig 2)

Figure 2—A young tertian parasite attaching itself to a fresh (unblanched) red corpuscle This parasite is pigmented and its thread-like processes can be seen fastened onto the corpuscle, one process along the edge of the corpuscle, the other on its surface between the corpuscle and the glass slide beneath The good condition of the corpuscle indicates that the parasite is coming rather than going (see Plate VII, Fig 3)

Figure 3—A young pigmented tertian parasite, which has recently attached itself to the surface of an apparently healthy corpuscle (by *careful focussing* the thread-like processes of cell-protoplasm could be seen on the surface of the corpuscle) Same points proved as in Figures 1 and 2, but at a more advanced stage of the parasite's attachment (see Plate VII, Fig 4)

Figure 4—A group of young tertian parasites, resulting from a parasite segmenting free in the blood-serum Note that these parasites are much smaller than the invading parasites shown in Figures 1, 2 and 3, and that they are not pigmented (the black dots are nuclei and not pigment) These parasites have not as yet started on their independent existence

Figures 5 to 12—Destruction of corpuscles by parasites in *varying* stages of development

Figures 5 6 and 7—Young parasites which have almost completely destroyed the corpuscles to which they are attached In Figures 5 and 7, the corpuscular remains (*a*) can be easily seen In Figure 6, these remains are less clearly seen as a dimming at *a* and the parasite seems to be attaching itself to a fresh corpuscle by means of the processes of cell-protoplasm If these parasites are not to perish they must migrate Note how enormously the red corpuscle is distended in Figure 7 This corpuscle is occupied by two young parasites In this group Figure 5 corresponds to Plate VII, Figure 12

Figures 8 and 9—Two tertian parasites whose stages of development are more advanced than those of the parasites seen in Figures 1 to 7 The corpuscular remnants in connection with these parasites can be seen at *a* if the pictures are carefully examined

Figure 10—A large tertian parasite which has destroyed the corpuscle to which it is attached until nothing but the corpuscular shell remains This parasite is probably about to migrate Note the large size of the degenerated corpuscle

Figure 11—A parasite still attached to the corpuscular remnant which can be seen at *a*

Figure 12—Three parasites in the same stage of development one attached to an apparently healthy corpuscle (which it has probably just invaded) while the other two still remain with the faintly staining degenerated corpuscular remnants seen at *a*

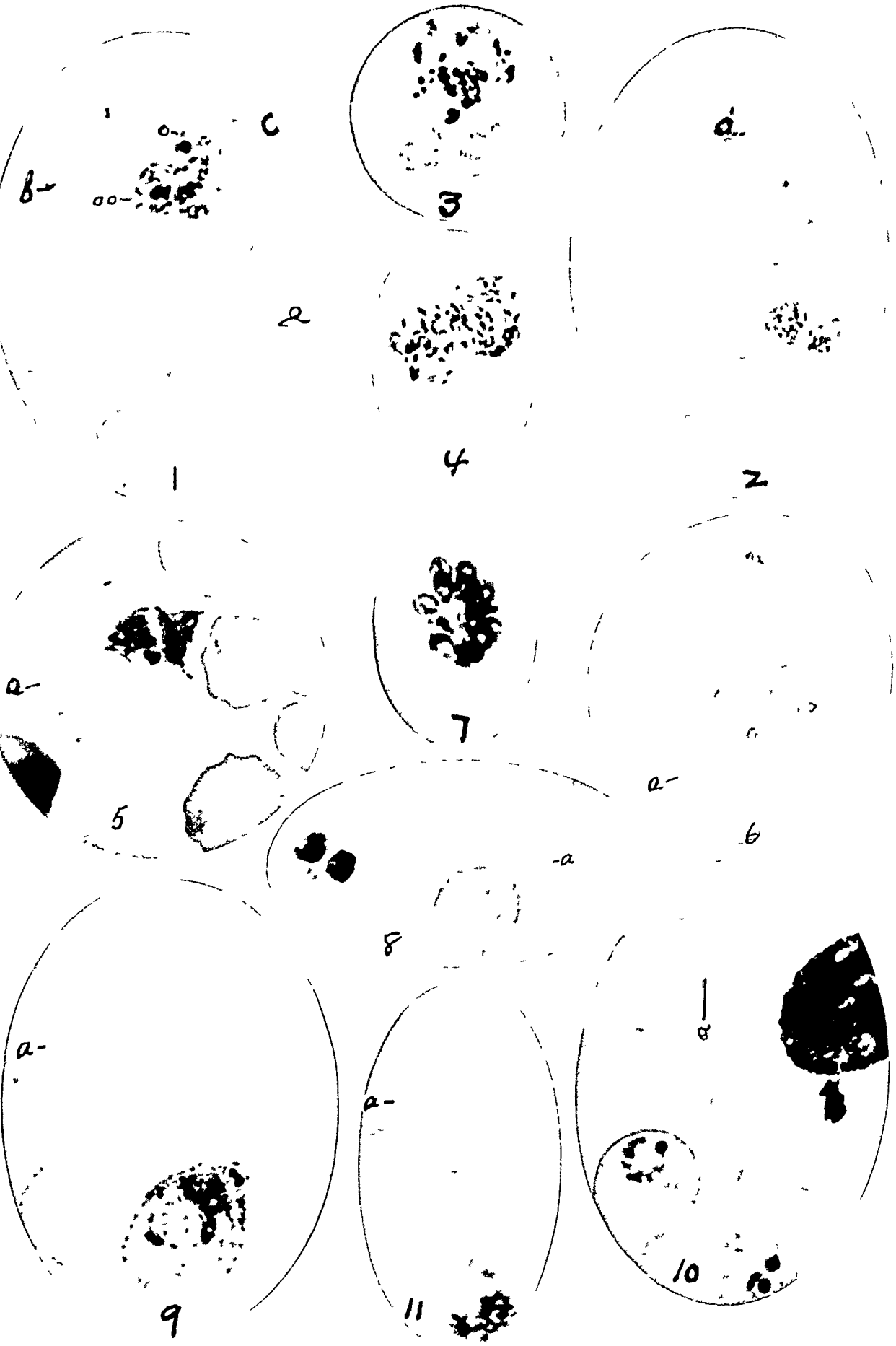

PLATE II

Plate II —Case 1 (continued) Figure 11, from a case of estivo autumnal infection, × 2000 Figures 1 to 10, magnification × 1850

Figure 1 —Two tertian parasites (multiple infection) of different ages (*o* and *oo*) attached to a degenerated corpuscular remnant (*b*) The granular structure of the degenerated corpuscle is clearly shown Note the appearance of a double border at *c* At *a* is seen the remains of a slightly enlarged corpuscle showing structure similar to *b*, but not nearly so much expanded, and containing no parasite

Figure 2 —A free tertian parasite The corpuscular remnant at *a* has perhaps just been abandoned by the parasite, as the parasite is in close proximity to it This parasite is in the same stage of development as the parasite *oo* in Fig 1

Figure 3 —Two small parasites and a presegmenting organism on a corpuscle which shows degenerative changes similar to those seen in Fig 1 (see Plate VII, Figure 10)

Figure 4 —Two presegmenting parasites on an apparently healthy corpuscle I believe these parasites have but recently attached themselves to the corpuscle, because the hemoglobin has not been bleached out

Figure 5 —Another instance of corpuscular destruction by an adult parasite (not mature) The parasite shows delicate filaments of cell protoplasm which go over the periphery of the corpuscle and embrace it The corpuscle is seen to be in the same stage of destruction as is the one in Fig 1 (see Plate VII, Figure 11)

Figure 6 —Multiple infection of a degenerated corpuscle by young parasites Additional evidence of the destruction of corpuscles by parasites which have not yet reached maturition In wet preparations, might not parasites similarly set free from the corpuscle, give the appearance of fragmentation?

Figure 7 —A segmenting body Note the small size of the corpuscle to which the parasite is attached, as compared with the expanded corpuscles in Figures 1 and 2 Note also the absence of granulation in the corpuscle This figure represents what is currently supposed to be the only way in which corpuscles are destroyed i e, by the ripening of the parasite

Figures 8 (Plate VII, Figure 16) 9 and 10 —Parasite free corpuscular remnants, resulting from the destructive action of the tertian parasites Note the similar structure in all these corpuscular remnants

Figure 11 —Corpuscular remnant from a case of estivo autumnal infection

PLATE III

Plate III —Case 1, continued, Figures 1 to 26 and 28, magnification × 1850 Figure 27 × 1600

Figure 1 —A young parasite, the product of a recent segmentation This parasite is not pigmented and has not yet attached itself to a corpuscle

Figure 2 —A free parasite, slightly smaller than Figure 1, but containing fine pigment granules (to the right), showing it has had a previous attachment to a corpuscle

Figures 3 to 10 —Free parasites in varying stages of development

Figure 11 —Two parasites free in the blood serum At *a* can be seen a small parasite without any pigment in its protoplasm

Figures 12 to 15 —Parasites free in the blood serum Figure 14 shows a delicate filament arising from the cell protoplasm of the parasite

Figure 16 —Two free parasites At *a* can be seen a small parasite which was set free before it had time to secrete pigment

Figures 17 to 20 —Parasites free in the blood serum

Figure 21 —Here, for the purpose of comparison, are placed side by side parasites (in the upper section, *a*) which are the result of a recent segmentation and whose protoplasm contains no pigment (the pigment set loose by the process of segmentation can be seen in the form of black dots at the upper part of the picture), and (in the lower section, *b*), parasites set free by the destruction of the corpuscle which they had occupied Note that the protoplasm of this set of free parasites contains fine pigment granules

Figures 22 to 25 —Adult parasites free in the blood plasma

Figures 26 and 28 —Attached and unattached parasites are seen side by side

Figure 27 —A nucleated red corpuscle (normoblast) and a corpuscle infected by two parasites This figure is shown to give an idea of the severity of the anemia present at the time the smear was taken which contained the free and nearly free parasites pictured in Case 1

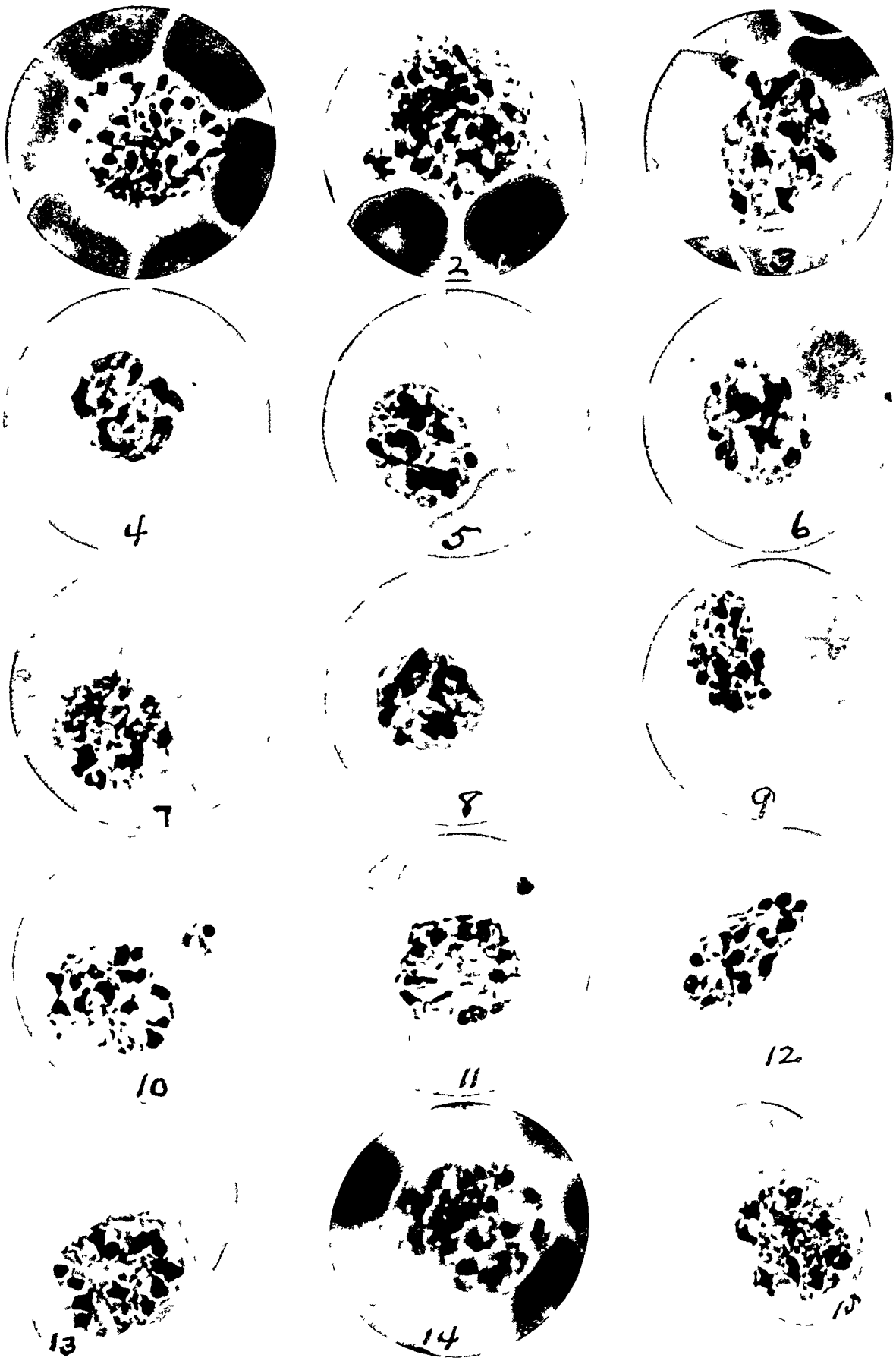

PLATE IV

Plate IV —Case 2 Tertian malaria Magnification × 1850 Giemsa stain This plate is designed to show segmenting and presegmenting bodies (a) on healthy (recently invaded) corpuscles, (b) on anemic corpuscles, and (c) free in the blood plasma All these figures were photographed from a single smear If parasites always matured within a single corpuscle, these three sets of phenomena could not occur in the same smear

Figures 1 and 2 —Segmenting bodies with the corpuscles almost destroyed The protoplasm of the parasites has formed itself into segments In Figure 2 note the granular and expanded appearance of the infected corpuscle This condition is rare in corpuscles infected by segmenting parasites and resembles closely the appearance of the corpuscular remnants with parasites attached as seen in Figures 1 and 5, Plate II

Figure 3 —A presegmenting parasite (wherein the protoplasm has not formed itself into distinct segments) attached to a degenerated corpuscle This parasite shows a stage of development similar to the parasites free from corpuscles in Figures 4 to 12 It has probably nearly reached the stage of migration (see Plate VII, Figure 5)

Figures 4 to 12 —Presegmenting parasites free in the blood serum (Figure 5 corresponds to Plate VII, Figure 6)

Figures 13 (Plate VII, Figure 7) and 15 —Parasites in the presegmenting stage attached to apparently healthy corpuscles The parasites have probably just attached themselves to the corpuscles and have not had time to do much damage

Figure 14 —The protoplasm of the segmenting body has formed itself into distinct segments while yet the corpuscle to which it is attached is still fairly healthy

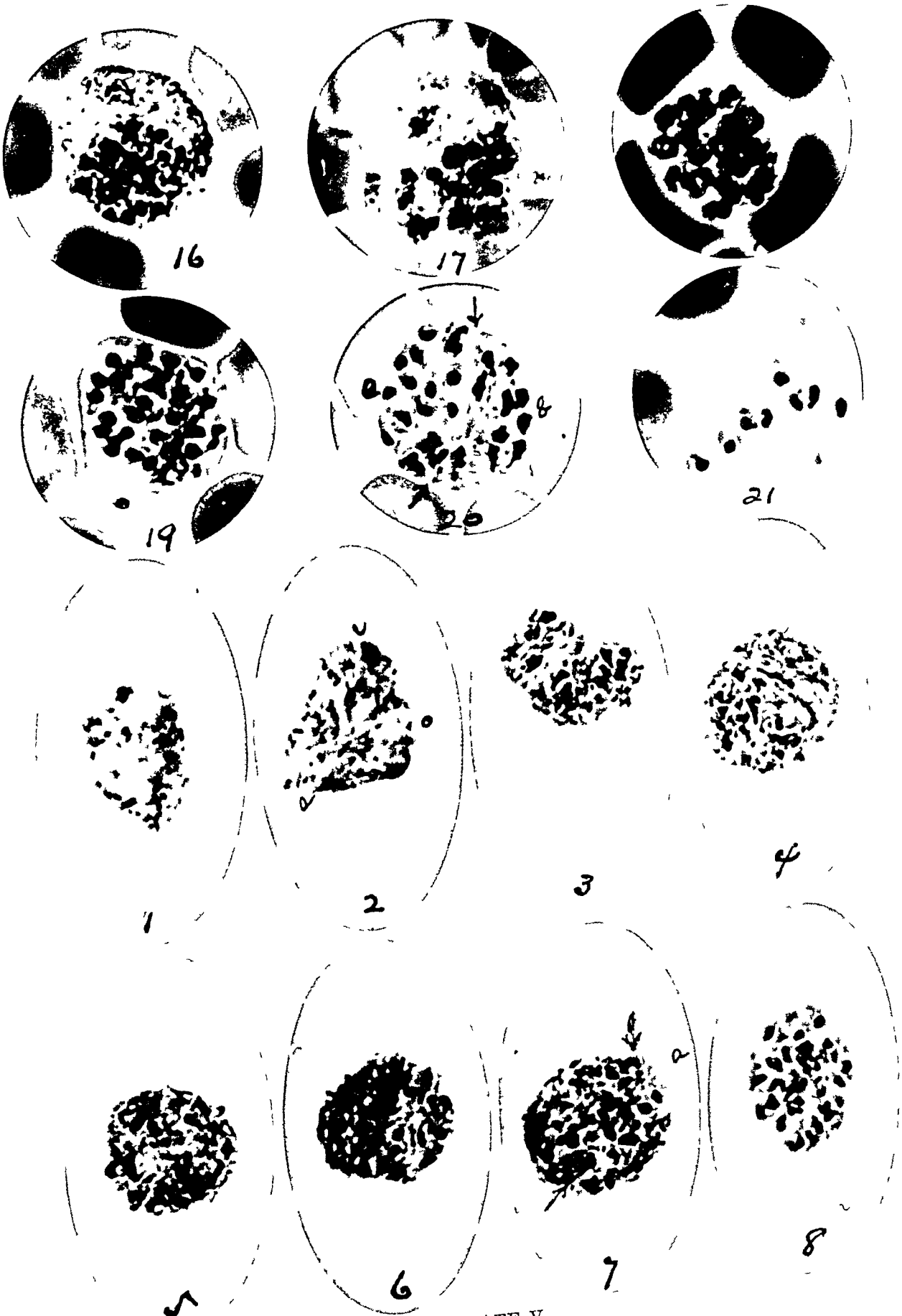

PLATE V

Plate V —Figures 16 to 21, continuation of Case 2 (Giemsa stain) Magnification ×1850 Case 3, Figures 1 to 8, magnification × 1850 (Wright's modification of Leishman's stain)

Figure 16 —A corpuscle infected by a presegmenting parasite (below) and a half-grown parasite (above) This corpuscle shows Schuffner's granulations (Plate VII, Figure 9)

Figure 17 —A corpuscle infected by a segmenting body (below) and a half-grown parasite (above) This corpuscle also shows Schuffner's granulation

Figure 18 —A segmenting parasite The corpuscle is almost destroyed

Figure 19 —A presegmenting parasite, 25 "spores" (above) and a small unpigmented parasite (in the lower portion of the corpuscle) on a fairly healthy corpuscle (Plate VII, Figure 8)

Figure 20 —Two parasites free from the corpuscle, a segmenting body at *a* and at *b*, a presegmenting parasite A careful examination of the picture will show, between the arrows, the division between the parasites In the portion on the left the segments are completed, the right portion shows the protoplasm of the parasite has not yet formed itself into segments The parasites are so grouped as to closely resemble one large segmenting parasite (a result of the multiple infection of a single corpuscle by parasites of varying ages)

Figure 21 —Young parasites free in the blood-serum These parasites contain no pigment and are the result of a recent segmentation The black dots are nuclei

Figure 1 —An adult parasite free from a corpuscle

Figure 2 —Three adult parasites free from the corpuscle Their respective nuclei can be seen at *a*, *c*, and *o* A careful examination of the picture will show white lines of division between the parasites (the result of a triple infection of a single corpuscle)

Figures 3 to 7 —Presegmenting parasites free from corpuscles Figure 3, shows two parasites Figure 7 also shows two parasites, one partly overlying the other the overlying portion can be traced between the arrows At *a* curled up filaments of parasitic cell-protoplasm can be seen

Figure 8 —A segmenting body free from the corpuscle

PLATE VI

Plate VI —Case 4 Tertian malaria Magnification × 1850 Wright's modification of Leishman's stain

Figure 1 —A free parasite showing considerable pigmentation on the left especially (Plate VII, Figure 13)

Figure 2 —A free pigmented parasite just attaching itself to a fresh corpuscle by means of its delicate filaments of cell-protoplasm (one of these filaments contains two granules of pigment) The pigmentation of the parasite is evidence of a previous attachment (Plate VII, Figure 14)

Figure 3 —A free pigmented parasite with filaments arising from the cell protoplasm, in which filaments can be seen granules of pigment Note the resemblance of this parasite to many of the so-called flagellating bodies seen in wet preparations The pigmentation of the parasite is evidence of previous attachments (Plate VII, Figure 15)

Figure 4 —Two half-grown parasites on a healthy corpuscle The nuclei of the parasites in their achromatic (white) zones can be seen at opposite poles and are indicated by arrows

Figure 5 —An adult parasite on a degenerated corpuscle, faintly indicated below and to the left of the parasite This parasite must migrate soon or die

Figures 6 to 8 —Parasites in the same stages of development as the one seen in Fig 5, but entirely free from their corpuscles

Figure 9 —Two free parasites, one partly overlying the other (result of multiple infection) The respective nuclei of the parasites can be seen at *a* and at *c* Where the one parasite overlies the other can be seen between the arrows

Figure 10 —A presegmenting parasite with the corpuscular remains very faintly seen above and to the right of the parasite

Figures 11 to 15 —Presegmenting parasites free from corpuscles Figure 14 shows two presegmenting parasites close together suggesting previous attachments to the same corpuscle

Figures 16 and 17 —Presegmenting parasites on somewhat degenerated corpuscles, note how much less degenerated these corpuscles are as compared with the corpuscle in Figure 5, to which is attached a younger parasite

Figure 18 —A segmenting body free from a corpuscle

moved on to another corpuscle, leaving the corpuscular remnants free in the blood-serum In cases of rich malarial infections, in which the blood contains many parasites, certain of the smears taken during the developmental cycle will be found to contain numerous examples of these injured corpuscles Dr Andrew Balfour refers, with illustration, to these remnants as "fragile red cells assuming half-moon and other peculiar shapes" He states that he has seen them in chronic malaria † These remnants are more easily recognized if the smear is so stained that the eosin tinge predominates (It is in such smears that Schuffner's dots are also well shown)

In some cases of estivo-autumnal infections I have seen these corpuscular remnants enormously expanded, 30 to 35 microns in diameter

As already suggested, the majority of these "corpses" are irregularly ring-shaped, one portion of the ring being wider than the rest so that its general appearance is that of a crescent moon with the ends bent together One of the marks by which we may recognize these defunct corpuscles is in their tinctorial character With Wright's modification of Leishman's stain they take a delicate pink hue, similar to that of the corpuscular remnants to which parasites are still attached (Plate VII, Fig 16)

Occasionally a rare corpuscular shell, resembling these corpuscular remnants seen in malarial blood, is found in blood which does not contain malarial parasites, but never in such numbers as are seen in malarial blood Whether these remnants seen in non-malarial blood are remnants remaining from a long-past malarial infection or from some other cause, I am unable to state, but I do know that they may persist in the blood long after the parasites have disappeared from the peripheral circulation

ATTACHING-FILAMENTS ARISING FROM THE PROTOPLASM OF THE MALARIAL PARASITE

It may be well to call attention at this point to observations illustrating the way in which a parasite may attach itself to a corpuscle My pictures show, I believe, that certain parasites have thrown out prolongations of cell-protoplasm for the purpose of attaching themselves to a corpuscle (Plate I, Figs 2, 3, 6, Plate VI, Fig 2, and Plate VII, Figs 3 and 4) I believe that these processes, which are thrown out or drawn

† Balfour, A Fallacies and Puzzles in Blood Examination, Fourth Report (Vol a) Wellcome Tropical Research Laboratories, 1911, p 120

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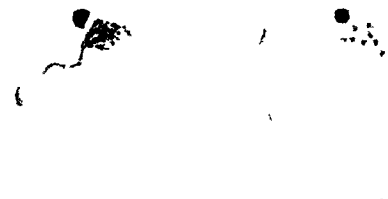

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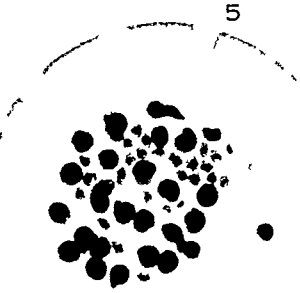

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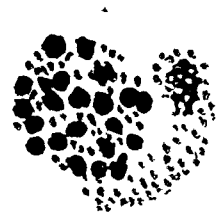

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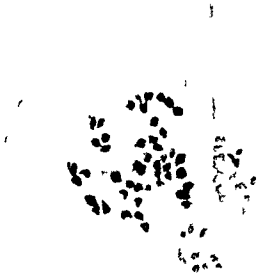

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PLATE VII

Plate VII —With the exception of Figure 1, these pictures are photographic duplicates of figures seen in the uncolored pictures These pictures were printed faintly on platinum paper and then colored

Figure 1 (corresponding to Figure 1, Plate III) —A free, unpigmented parasite resulting from a recent segmentation The absence of pigment suggests that the parasite has not yet attached itself to a corpuscle

Figure 2 (corresponding to Figure 1, Plate I) —A young pigmented parasite, free in the blood-serum, the pigmentation being evidence of a previous attachment to, and conquest of, a corpuscle

Figure 3 (corresponding to Figure 2, Plate I) —A young pigmented parasite just attaching itself to a corpuscle The unblanched condition of the corpuscle seems to prove that the parasite must have derived its pigment from a previous attachment to another corpuscle

Figure 4 (corresponding to Figure 3, Plate I) —A young pigmented parasite attached to a corpuscle by threads of protoplasm The pigment in the parasite was probably derived from another corpuscle

Figure 5 (corresponding to Figure 3, Plate IV) —A presegmenting parasite attached to a corpuscle which is almost destroyed This parasite is probably preparing to migrate

Figure 6 (corresponding to Figure 5, Plate IV) —A presegmenting parasite free in the blood-serum This parasite is probably in the act of migrating

Figure 7 (corresponding to Figure 13, Plate IV) —A presegmenting parasite on a healthy-appearing (unblanched) corpuscle This parasite has probably just landed from its last migration and has not had time to seriously damage the corpuscle

Figure 8 (corresponding to Figure 19, Plate V) —A presegmenting parasite and a small unpigmented parasite on a fairly healthy corpuscle These parasites have probably occupied the corpuscle but a short time

Figure 9 (corresponding to Figure 16, Plate V) —A double infection of a corpuscle by a presegmenting body and a half-grown parasite The corpuscle shows Schuffner's granulations All the half-grown parasites in this case were attached to corpuscles

Figure 10 (corresponding to Figure 3, Plate II) —A presegmenting parasite and two young parasites on a corpuscle which shows degenerative changes similar to those seen in the corpuscles in Figures 11 and 12 All other presegmenting parasites in this case were attached to healthy-appearing corpuscles

Figure 11 (corresponding to Figure 5, Plate II) —A healthy-appearing pigmented parasite attached to a degenerated corpuscle From the arrangement of the filaments, the parasite can be seen to be on the surface of the corpuscle This parasite must migrate if it requires further nourishment

Figure 12 (corresponding to Figure 5, Plate I) —Showing extensive destruction of a corpuscle by a parasite young in its development This parasite must also migrate or perish for want of food

Figure 13 (corresponding to Figure 1 Plate VI) —A young parasite containing a large amount of pigment The pigmentation suggests that this parasite must have been attached to a corpuscle

Figure 14 (corresponding to Figure 2, Plate VI) —A parasite, pigmented, and free in the blood plasma It can be seen to have delicate filaments which apparently are just fastening onto a fresh corpuscle The pigmentation is evidence of a previous attachment

Figure 15 (corresponding to Figure 3 Plate VI) —A free, pigmented parasite The processes of cell protoplasm contain granules of pigment This parasite has derived its pigment from an attachment to a corpuscle

Figure 16 (corresponding to Figure 8 Plate II) —A parasite free corpuscular remnant found in a tertian infection

in at will, are used for the purpose of capturing as well as for securing attachment to their prey [20]

In some instances (Plate II, Fig 5, and Plate VII, Fig 11), these protoplasmic processes can be seen to extend beyond the periphery of the corpuscle, so that the parasite seems to embrace the corpuscle This illustration clearly shows that the parasite is on the surface of the corpuscle and not within its substance [23]

I have seen several instances in which a parasite seemed to be attaching itself to a fresh corpuscle before it had altogether abandoned the moribund one (Plate I, Fig 6) Dock[12] has observed that "even before the final disappearance of the corpuscle a filament may form on the plasmodium"

These filaments, or prolongations, which may or may not contain pigment, always arise from the protoplasm of the parasite, never from the nuclear material A parasite with these prolongations of cell-protoplasm, if seen free from a corpuscle in the blood-serum (Plate V, Fig 3, and Plate VII, Fig 14), may closely resemble some of the so-called "flagellating bodies" seen in moist-chamber preparations

Undoubtedly many of the so-called "flagellating bodies" seen in fresh blood preparations are parasites armed with protoplasmic processes for securing attachment to a corpuscle True flagella (fertilizing elements) never arise from the protoplasm of the parasite, but are always derived from the chromatin-substance of the malarial parasite and from the chromatin-substance alone This is true in all malarial infections, tertian and quartan, as well as in estivo-autumnal infections [25]

The protoplasmic processes of the malarial parasites, in the majority of cases, contain pigment granules, while it is extremely rare to find any

20 Investigations carried on by Lèger[21] and others have demonstrated that the supposed ameboid processes of certain protozoa, the schizogregarinæ, serve more as attaching organs and for the purpose of absorbing food than for the purpose of locomotion

Calkins[22] states that "The spores of the myxosporidia are provided with 'anchoring threads' for the purpose of attaching themselves externally to certain cells" And it is well known that many ameba use protoplasmic processes for the purpose of capturing their prey

21 Lèger Quoted from Calkins, Protozoology, 1909, p 57

22 Calkins The Protozoa, 1907

23 One of the arguments urged by Marchiafava and Celli[24] in favor of the intracellular theory of the malarial parasite is that the pseudopodia of the ameba never extended beyond the limits of the red corpuscle, which must have occurred were the parasite merely attached to it, hence the parasite must be within the substance of the red corpuscle

24 Marchiafava and Celli Quoted from Marchiafava and Bignami Parasites of Malarial Fevers, 1894, p 188

25 In a previous research, published in the Jour Exper Med, Feb 1, 1911, I have recorded the occurence of a sexual cycle in the circulating blood of man in estivo autumnal infections Studies on the sexual cycles of parasites of tertian and quartan infections are now in preparation for publication

trace of pigment outside the body of the parasite in connection with true flagella (microgametes) This conclusion was reached after the study of over 200 flagellating parasites (microgametocytes) found in stained specimens of newly drawn and immediately dried blood of the several malarial infections

MULTIPLE INFECTION IN RELATION TO MIGRATION

Multiple infection of a red corpuscle by two or more parasites is not uncommon If they do not all grow up on one corpuscle, what becomes of them? One of the theories advanced as to the ultimate fate of the young parasites of a double infection is the so-called intracorpuscular conjugation Ewing[26] in discussing this question mentions seeing a specimen of blood from a tertian infection "in which there were very numerous twin parasites of a younger brood while all the older parasites were single" He explains the disappearance of the "twins" and the appearance of the "older single parasites" by the theory of conjugation This hypothesis is supported by Craig[27] and Wright,[28] but has not, I believe, been confirmed by subsequent observers, and it seems to me that the migration of the parasites to other corpuscles is a more probable explanation, for the conjugation theory would not account for the final disposition of "triplets" (Plate V, Fig 2), or that of parasites of varying ages occupying one corpuscle (Plate II, Figs 1 and 3, Plate V, Figs 16, 17, 19, 20, and Plate VII, Figs 8, 9, 10)

The occurrence of multiple infection by young parasites might be explained by the following supposition

When a parasite segments, leaving the young "spores" grouped together but free to attach themselves to corpuscles (Plate I, Fig 4, Plate III, Fig 21a, Plate V, Fig 21), it is not surprising that two or more of these youngsters should try for and capture the same corpuscle Later in their life-history, during migrations, when the parasites are more equally distributed, the chances are fewer that more than one parasite will infect a single corpuscle

Various problems are suggested by this study

1 One might measure as accurately as possible the havoc produced by each parasite (i e, the number of corpuscles destroyed by each invader) during its life cycle, if one studied smears taken at frequent intervals during the developmental cycle of the parasite I am now at work on this problem and shall publish my findings later

2 What becomes of the corpuscular remnants? I do not believe that

26 Ewing Clinical Pathology, 1908 p 154

27 Craig Observations Upon Malaria Latent Infections in Natives of the Philippine Islands — Intracorpuscular Conjugation Philippine Journ of Sc 1906 1 525

28 Wright Quoted from Calkins Protozoology 1910 p 287

they can be wholly eliminated by the phagocytes In successive attacks of malaria without adequate treatment, might not these remnants accumulate and create serious disturbances in the system of the patient?

CONCLUSIONS

The grave and rapid anemia occurring in some malarial infections can easily be explained as due to the migration of parasites of all ages from corpuscle to corpuscle The evidence presented in this paper would seem to justify this belief The most important fact supporting it is the frequent finding of parasites in similar stages of development, (1) free, with varying amounts of pigment included in their substance, (2) on healthy corpuscles (corpuscles showing abundant hemoglobin and no evidence of degeneration), (3) on corpuscles which show conclusive evidence of degeneration

The fact that parasites in each and every stage of development may be seen on healthy corpuscles would seem to be conclusive evidence of migration For a parasite could not receive nourishment and secrete pigment (if that pigment be derived from the red corpuscle) and complete its life cycle on a single corpuscle without that corpuscle showing conclusive evidence of degeneration

The fact that young parasites are seen on corpuscles with an almost complete loss of hemoglobin (Plate I, Figs 5 and 7), would seem to indicate that the parasite must migrate or perish for lack of food

Still another support for my hypothesis is found in cases of multiple infection, in which three or four young parasites (sometimes six or seven) are attached to a corpuscle We can hardly expect that all these youngsters can grow up on a single corpuscle, and if they are not to perish, they must migrate

I wish to express my warm appreciation of the advice and assistance given me during the prosecution of this study by Dr William T Councilman and Dr Richard C Cabot of Harvard University, and to express my indebtedness to Dr Daniel Sullivan of New London, Conn, for material, and to Dr Stuart J Lawson of New London, Conn, for the photographs

THE GLYCYLTRYPTOPHAN AND TRYPTOPHAN TESTS FOR CANCER OF THE STOMACH

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Muller's work[1] suggested that malignant tumors contain one or more proteolytic enzymes Emerson,[2] Fischer[3] and many others have shown that such is the case Recently Neubauer and Fischer[4] and Abderhalden and his associates[5] have found that malignant growths contain an enzyme capable of splitting certain polypeptids into amino-acids Neubauer and Fischer[4] have introduced, on this basis, the so-called "glycyltryptophan test" for carcinoma of the stomach

Lyle and Kober[6] regarded the glycyltryptophan test as a very good one, especially if more than two tests on every case are carried out Weinstein[7] has shown that the use of glycyltryptophan is unnecessary for the detection of a tryptophan-producing enzyme in gastric contents, since gastric contents always contain proteoses and peptones that are easily convertible by cancer enzyme into their hydrolytic products, among which tryptophan would be included Therefore it is unnecessary to add a

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*Shortly after the appearance of Dr Weinstein's first paper in this connection (See Note 7), Dr Sanford, working at the German Hospital, made several tests with glycyltryptophan and with stomach contents direct, with results that did not agree with Dr Weinstein's main conclusions At that time I was an associate in this laboratory on the Crocker Foundation and also, by courtesy of the committee in charge of the Crocker Special Research Fund, pathological chemist at the German Hospital When Professor Gies was informed that Dr Sanford's tests did not agree with Dr Weinstein's findings Professor Gies encouraged us to proceed with and to extend, the work on the ground that the whole truth in any matter is a prime object of scientific endeavor We continued, with this encouragement at the German Hospital and in this laboratory, and have obtained the results here recorded Professor Gies provided glycyltryptophan from the supply with which he furthered Dr Weinstein's work and which was obtained under the auspices of the George Crocker Special Research Fund Jacob Rosenbloom Biochemical Laboratory, College of Physicians and Surgeons

1 Muller Ztschr f klin Med 1889 xvi, 196

2 Emerson Deutsch Arch f klin Med 1902 lxxii 415

3 Fischer Deutsch Arch f klin Med 1908 xciii 98

4 Neubauer and Fischer Deutsch Arch f klin Med 1909, xcvii, 499

5 Abderhalden and Rona Ztschr f physiol Chem 1909, lx 515 Abderhalden Koelker and Medigreceanu Ztschr f physiol Chem 1909 lxii 135 Abderhalden Ztschr f physiol Chem 1909 lxii 136

6 Lyle and Kober New York Med Jour 1910 xci 1151

7. Weinstein Jour Am Med Assn 1910 lv 1087

dipeptid as a means for the detection of the cancer enzyme Weinstein tests for tryptophan in the stomach contents, directly and after incubation

Hall and Williamson[8] have lately asserted that tryptophan does not appear in stomach contents with Ewald test-meals either before or after incubation It does occur before and after incubation when a meat test-meal is given, but does not show any relation to carcinoma They conclude that the tryptophan test is valueless if the polypeptid is not added to the gastric contents

Kuttner and Pulvermacher[9] have advocated the use of *Seidenpeptone* and have shown that comparative tests with glycyltryptophan paralleled each other accurately The tyrosin formed by the cancer enzyme from *Seidenpeptone* is recognized microscopically

Other studies with the glycyltryptophan test have been carried out by Ley,[10] Pechstein,[11] Ehrenberg,[12] Oppenheimer,[13] Kohlenberger[14] Further studies have been conducted by Neubauer and Fischer,[15] who found that 84 per cent of gastric cancer cases verified by autopsy gave positive reactions with the glycyltryptophan test, also that 75 per cent of the clinical cases of gastric cancer, as well as 15 per cent of stomach conditions that were not cancerous, gave the test

One of the most striking things about the glycyltryptophan test has been the wide difference of opinion regarding its value Some pronounce it very good, others maintain that it is valueless and that glycyltryptophan in stomach contents yields tryptophan in a large number of cases in which no cancer exists The wide divergence of opinion may now be explained on the basis of Warfield's[16] findings, who has shown that the saliva of several persons, when not materially acid (to litmus) to begin with has the power of decomposing glycyltryptophan into its constituent amino-acids Warfield's results make it evident that swallowed neutral or alkaline saliva (to litmus), when mixed with neutral or faintly acid gastric contents, imparts to the latter the power of producing tryptophan from glycyltryptophan, thus rendering the glycyltryptophan test of doubtful value in any instance, if not wholly vitiating it

Weinstein[17] has verified Warfield's findings and concludes that although Warfield's results discredit the glycyltryptophan test, they do not depreciate the value of the "tryptophan" test, because the salivary

8 Hall and Williamson Lancet, London, 1911, clxxxi, 731, Jour Path and Bacteriol, 1910, xv, 352
9 Kuttner and Pulvermacher Berl klin Wchnschr, 1910, xlvii, 2057
10 Ley Berl klin Wchnschr, 1911, xlviii, 119
11 Pechstein Berl klin Wchnschr, 1911, xlviii, 375
12 Ehrenberg Berl klin Wchnschr, 1911, xlviii, 704
13 Oppenheimer Deutsch Archiv f klin Med, 1910 11, ci, 293
14 Kohlenberger Deutsch Arch f klin Med, 1910, xcix, 148
15 Neubauer and Fischer Munchen med Wchnschr, 1911, lviii, 674
16 Warfield Bull Johns Hopkins Hosp, 1911, xxii, 150
17 Weinstein Jour Am Med Assn, 1911, lvii, 1420

TABLE 1.—EIGHTY TESTS CARRIED OUT ON THIRTY-EIGHT PATIENTS

No.	Date of 1910	Ewald Test-Meal	Full Meal	Glycyl-tryptophan Test	Contents After Incubation, Tryptophan Test	Clinical Diagnosis	Stomach Contents Total Acidity	Stomach Contents Free HCl	Remarks
1	10/12	+			—	Pernicious anemia	30	0	
	10/14		+		—	Pernicious anemia	35	0	
2	10/12	+			—	Rheumatic myositis	35	0	
	10/14		+		—	Rheumatic myositis	40	0	
3	10/13	+			—	Mass in right hypochon region			Mass is suggestive of carcinoma
	10/15		+		—	Mass in right hypochon region			
4	10/14	+			—	Pulmonary tuberculosis			
	10/15		+		—	Pulmonary tuberculosis			
5	10/14	+			—	Cholelithiasis			
	10/15		+		—	Cholelithiasis			
6*	10/14	+		+	+	Gastric crisis of tabes	90	40	Laparotomy showed a dilated stomach
	10/15		+	+	+	Gastric crisis of tabes	85	50	
	10/29	+		—	—	Gastric crisis of tabes	80	35	At this time patient was free of the gastric pains
	10/30		+		—	Gastric crisis of tabes	85	48	At this time patient was free of the gastric pains
7	10/16	+			—	Gastric neurosis			
	10/17		+		—	Gastric neurosis			
8	10/17	+			—	Gastric neurosis			
	10/18		+		—	Gastric neurosis			
9	10/17	+			—	Cirrhosis of the liver	60	20	
	10/18		+		—	Cirrhosis of the liver	50	10	
10	10/20	+			—	Gastric neurosis	90	30	
	10/21		+		—	Gastric neurosis	80	30	
11	10/20	+		—	—	Carcinoma of stomach	40	0	Operation showed carcinoma at the pylorus
	10/22		+	—	—	Carcinoma of stomach	30	0	

No Case	Date 1910	Ewald Test-Meal	Full Meal	Glycyl-tryptophan Test	Contents After Incubation Tryptophan Test	Clinical Diagnosis	Stomach Contents Total Acidity	Stomach Contents Free HCl	Remarks
12	10/22	+		—	—	Carcinoma of stomach	30	0	Autopsy showed carcinoma of the stomach
	10/23		+	—	—	Carcinoma of stomach	40	0	
13	10/23	+			—	Carcinoma of uterus	50	10	
	10/24		+		—	Carcinoma of uterus	60	25	
14	10/23	+			—	Carcinoma of uterus			
	10/24		+		—	Carcinoma of uterus			
15	10/25	+			—	Pneumonia			
	10/26		+		—	Pneumonia			
16	10/25	+			—	Typhoid fever			
	10/26		+		—	Typhoid fever			
17	10/27	+		—	—	Carcinoma of stomach	40	10	Operation showed an old ulcer with constriction of the pylorus
	10/28		+	—	—	Carcinoma of stomach	45	20	
18	10/28	+		—	—	Carcinoma of the uterus			
	10/29		+		—	Carcinoma of the uterus			
19	10/29	+		—	—	Carcinoma of breast			
	10/30		+		—	Carcinoma of breast			
20	11/12	+		—	—	Carcinoma of stomach	65	0	Operation showed extensive carcinoma of the stomach
	11/13		+	—	—	Carcinoma of stomach	60	0	
21	11/12	+		—	—	Carcinoma of stomach	80	0	
	11/13		+	—	—	Carcinoma of stomach	70	0	
22	12/29	+			—	Gastroptosis	40	0	
	12/30		+		—	Gastroptosis	40	0	
23	12/28	+		—	—	Carcinoma of stomach	35	0	
	12/29		+		—	Carcinoma of stomach	40	0	
	12/30		+		—	Carcinoma of stomach	40	0	
24	12/29	+			—	Atonic dilatation of stomach			
	12/30		+		—	Atonic dilatation of stomach			
	1911								
25	1/ 5	+		+	+	Hypernephroma	70	20	Diagnosis verified at operation
	1/ 6		+	+	+	Hypernephroma	80	25	

				+	+				
26	1/ 2	+			—	Gastroptosis	60	20	
	1/ 3		+		—	Gastroptosis	70	30	
27	1/ 5	+		—	—	Carcinoma of stomach	40	0	
	1/ 6		+	—	—	Carcinoma of stomach	35	0	
28	1/ 7	+			—	Pulmonary tuberculosis	40	0	
	1/ 8		+		—	Pulmonary tuberculosis	50	0	
29	1/ 7	+			—	Lead poisoning	60	0	
	1/ 8		+		—	Lead poisoning	50	0	
30	1/ 8	+			—	Lymphatic leukemia	50	20	
	1/ 9		+		—	Lymphatic leukemia	45	20	
31	1/20	+		—	—	Carcinoma of stomach	40	0	
	1/21		+	—	—	Carcinoma of stomach	50	0	
32	1/29	+			—	Carcinoma of stomach	15	0	At operation extensive carcinoma of stomach Inoperable
	1/30		+	—	—	Carcinoma of stomach	20	0	
33	2/10	+		—	—	Carcinoma of stomach	30	0	At operation extensive carcinoma of stomach
	2/12		+		—	Carcinoma of stomach	40	0	
	2/16	+			—	Carcinoma of stomach	70	0	
34	2/17	+		+	+	Carcinoma of stomach	40	0	Operation showed carcinoma of stomach
	2/18		+		+	Carcinoma of stomach	50	0	
35	2/20	+		+	+	Carcinoma of stomach	45	0	Operation showed carcinoma of stomach
	2/21		+		+	Carcinoma of stomach	30	0	
36	2/24	+			—	Carcinoma of stomach	46	0	Operation showed carcinoma of stomach
	2/25		+	—	—	Carcinoma of stomach	50	0	
37	3/ 6	+			—	Carcinoma of stomach	46	0	Operation showed carcinoma of stomach
	3/ 7		+	—	—	Carcinoma of stomach	40	0	
38	3/ 9	+			—	Carcinoma of stomach	50	0	Operation showed carcinoma of stomach
	3/ 9		+	—	—	Carcinoma of stomach	46	0	

*Stomach contents from Case 6 gave positive glycyltryptophan and tryptophan tests during the time the patient had severe gastric pain On account of the clinical diagnosis an exploratory operation was carried out, which showed only a dilated stomach Two weeks later, when the patient was free from gastric pain, the tests were not obtained The patient was then found to have locomotor ataxia and we think the positive tests were due to the regurgitation of duodenal liquid (although the stomach contents gave no reaction for bile) on account of the violent gastric pain

peptidase does not produce tryptophan from the proteins in non-cancerous gastric contents.

Our results with the glycyltryptophan and tryptophan tests are presented below

The tests were carried out as follows One to two hours after the Ewald test-meal or a full meal, the stomach contents were withdrawn by siphonage Undue manipulation of the tube was avoided, for intragastric movement may lead to the reflex regurgitation of duodenal liquid The stomach contents were filtered and tested for blood, bile and tryptophan One part of the filtrate was added to a solution of glycyltryptophan and incubated for twelve, twenty-four or forty-eight hours at from 38 to 40 C Another portion of the filtrate was incubated directly Some of the glycyltryptophan solution used for the test was also incubated, and thus served as a control for free tryptophan in the glycyltryptophan solution used for the test Each portion of the incubated solutions was finally acidified with acetic acid (3 per cent) and then bromin water was added drop by drop In the presence of free tryptophan, a lilac color develops when a sufficient amount of bromin water is added The color disappears in a pronounced yellow when the bromin is present in excess, whereas in the absence of free tryptophan, the fluid acquires a pale yellow tint [18]

Table 1 contains the results of eighty tests carried out on thirty-eight patients [19] We carried out at least two tests in each case, after an Ewald test-meal and a full meal, respectively

Table 2 summarizes the results that we have obtained with the tryptophan and glycyltryptophan tests

TABLE 2.—SUMMARY OF RESULTS OBTAINED WITH TRYPTOPHAN AND GLYCYLTRYPTOPHAN TESTS

	Positive		Negative	
	Glycyltryptophan	Tryptophan	Glycyltryptophan	Tryptophan
Cancer of the stomach, verified by operation or post mortem	2	2	9	9
Cancer of the stomach, clinical diagnosis*	—	—	5	5
Other diseases than cancer of the stomach	2	2	—	20

*Case 17, which clinically suggested carcinoma of the stomach, gave negative tests and operation showed an old ulcer with constriction of the pylorus

Dr Weinstein has reported a few results which led him to conclude that the peptidolytic enzyme in saliva is unable to produce tryptophan

18 The incubated material should be filtered before testing for tryptophan, especially when a small amount of tryptophan has been produced We have found that the unfiltered material may react negatively, when, if filtered, the filtrate gives a faint reaction for tryptophan Dr Weinstein has also emphasized this point

19 We have never obtained a reaction for tryptophan in the stomach contents of any of this series of cases immediately after the contents were withdrawn, i e, before incubation

from Witte peptone, even after seven days' incubation in the presence of toluol

We have found, on the contrary, that the salivary peptidase may produce tryptophan from Witte "peptone" and also from casein We have also observed that this enzyme was absent from some specimens of saliva which were not acid to litmus to begin with From these observations it is hard to believe that the presence of peptidase in swallowed saliva vitiates the glycyltryptophan test without affecting the validity of the tryptophan test One would think that both tests are thus rendered unreliable, for proteoses and peptone are naturally present in the stomach contents after all test-meals We have also found that stomach contents from three individuals (two of them children), in whose cases there was no doubt that the stomachs were entirely free from carcinoma, contained tryptophan after incubation with saliva The positive reactions could not be obtained in these cases, unless the gastric contents were made neutral to litmus before the addition of the saliva, a result which may be explained by the fact that acidity prevents the salivary enzyme from acting In two other specimens of normal stomach contents, tryptophan was not produced when the tests were carried out in the same way as for those cases in which we obtained a positive reaction

Dr Weinstein states, in a footnote in his last paper, that "Dr Gies, although suggesting the probability of ereptic and tryptic excretion by the salivary glands, thinks it possible also that the tryptophan-producing enzyme in mixed saliva is derived in part from bacteria in the mouth, especially from cavities in carious teeth He has planned to investigate these possibilities" The variability of the results to which we refer in the preceding paragraph accords with this view of the situation

We agree with Dr Weinstein that the use of glycyltryptophan is unnecessary for the detection of tryptophan-producing peptidase in gastric contents, but our findings do not permit us to believe that the tryptophan test is a reliable one for gastric carcinoma

ARTIFICIAL PNEUMOTHORAX AS A TREATMENT OF PULMONARY TUBERCULOSIS

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Artificial pneumothorax therapy consists in the repeated injections of a slowly absorbable gas into the pleural cavity to permit and maintain for an indefinite period the collapse of a diseased lung

The investigations which form the basis of this paper were undertaken to determine the exact contributory value of this treatment, and although equally willing to deny the efficacy of the method, should our result so persuade us, we conclude on the contrary that the establishment of artificial pneumothorax is a procedure of unquestionable value in selected cases

The element of rest is now generally accepted as an important feature in the therapeutics of all tuberculous infections A striking example of this is found in the promptness with which an acute tuberculous infection of the hip or knee joint is quieted by rest from the application of a plaster cast The immobilization or splinting of a tuberculous lung, whether spontaneously or artificially produced, tends likewise to arrest the progress of the infection

It may be argued that Nature seeks to reduce the mobility of a phthisical lung by restricting the activity of the thoracic muscles of the infected side The affected chest becomes almost stationary, the normal convexity of its wall becomes flattened as the result of the approximation of the ribs A partial fixation of the lung thus results from the presence of the disease The general toxemia reduces the patient's ambition and activity, and recognizing that this may be an indication that Nature seeks thus to limit the progress of the disease, we have learned the importance of prescribing rest Together with the consequent diminished respiratory activity is associated reduced toxemia and an improvement in the general condition Contrasted with this is the apparent increased activity of a phthisical process prompted by the accelerated respiration resulting from physical exertion

The formation of a pleuritic exudate may be accepted as a further effort of the disease to combat itself Spengler, Adams, West, and Forlanini have emphasized the importance of respecting this condition, allowing the fluid to exert its compression on the lung, thus further immobilizing it While the removal of such fluid does not infrequently hasten death its retention has reduced fever, diminished the quantity of sputum,

and lessened toxic absorption A general improvement in the patient's condition has frequently followed

Spontaneous pneumothorax coincident to tuberculous necrosis and rupture of the lung was once regarded as a threatening occurrence in the course of pulmonary tuberculosis It is now considered to exercise in some cases a beneficial effect on the disease Spengler reports ten cases in which he recognized the possible value of this complication The exudate was allowed to accumulate until the level of the rupture was reached The accumulation of fluid seemed to favor the closure of the bronchial opening, and was withdrawn in small quantities when it became excessive In six of Spengler's ten cases complicated with hydrothorax and pyopneumothorax the patients recovered completely

Evidence is not lacking, therefore, that certain sequelæ of pulmonary tuberculosis act as self-limiting processes and apparently limit the disease by immobilizing and splinting the lung

The apparent beneficial effect of these processes when favored led to an attempt to produce them artificially Quincke, Spengler, Jordan, and Friedrich have resected large portions of many ribs to produce a partial collapse of the thoracic wall Immobilization and compression of the diseased lung has resulted with distinct improvement in such patients as have withstood the severe operation

Hydrothorax and pneumothorax have both been artificially produced with results which point unquestionably to the therapeutic value of such measures

ARTIFICIAL PNEUMOTHORAX

It is difficult and perhaps unnecessary to determine to whom priority should be credited in the conception of this therapeutic idea As to its application, suffice it to say that Forlanini and Murphy were apparently independently active in Italy and America In 1882 Forlanini published a statement to the effect that he was then at work to develop a suitable technic for the establishment of artificial pneumothorax In 1891 a publication indicated that he had already employed the treatment, presenting at the time a technic of administration In 1898 J B Murphy in the American Medical Association surgical oration independently contributed clinical results of this treatment with details of his method In the subsequent clinical application of artificial pneumothorax therapy Prof Ludolph Brauer has been conspicuously contributory Forlanini Spengler and Schmidt have also employed the treatment continuously Many other clinicians have reported their comparatively limited experience the German and Italian publications being predominant The work of Murphy was carried on by Dr Lemke up to his untimely death in 1901 the treatment has been employed [illegible]

The medical literature does not intimate that this inactivity may be regarded as an abandonment of the treatment by its supporters, inasmuch as there are no references even tending to discourage its applicability

PATHOLOGY

It is to be regretted that we have not a greater number of post-mortem records to show the exact nature of the pathological changes concurrent with this treatment Graetz reports the autopsy findings in three cases from Brauer's clinic He states that tuberculous cavities showed a marked diminution in size as compared with those outlined in the clinical findings previous to the first treatment The formation of connective tissue in the region of these cavities showed a tendency to cicatrization with contraction Cicatrization of the old isolated caseous areas was distinct, and the tendency to connective tissue formation around both the large and small tuberculous cavities was apparent, indicating that the infectious process had come to a point of quiescence, though complete healing did not yet exist Both the old and the new cavities were characterized by exceptionally slight content of tubercle bacilli There was a striking tendency to callus formation in the region of the vessels and bronchi, indicating the healing of perivascular and peribronchial inflammatory processes Graetz concludes as follows "There is no doubt in my mind that the anatomical changes in the lung must be regarded as proof that the tuberculous disease has come to a standstill and is in the process of healing" He associates this condition with the lung compression resulting from the artificial pneumothorax and believes that there is a certain relation between the extent of the connective tissue formation and the duration of the compression This extensive cicatrization of the tuberculous process which was marked in the lung previously subjected to compression was not present in like degree on the untreated side

There is and will doubtless continue to be a number of conflicting theories as to the probable explanation of this effect of pneumothorax on the tuberculous lung It must be admitted, however, that the compression alone is of paramount importance The cubical contents of the previously existing cavities are diminished, to which the concurrent diminution in the sputum quantity bears testimony The diminished amount of retained infectious material retards the activity of the tuberculous process, the immobility of the tissues lessening furthermore the transference of infectious material from one alveolus to another There is, moreover, a tendency to localize and encapsulate the smaller cavities

Changes in the blood and lymph circulation must also be accepted as contributory factors Czerniki credits the effect of pneumothorax to an anemia which results from the compression, as a result of which he argues that both the bronchial and cavity secretions are lessened It has been suggested furthermore, that a condition of passive hyperemia, as thera-

peutically produced by Bier, may take place There is not yet sufficient evidence that a distinct change in the pulmonary circulation occurs in the presence of pneumothorax to justify the acceptance of the circulatory theory. Animal experiments have been conflicting in this regard, and it is disputable as to whether the contracted lung contains more or less arterial or venous blood In fact, there is experimental evidence that the pulmonary circulation adapts itself promptly to the change and is therefore not particularly disturbed

There are reasons for believing that changes in the lymph circulation are responsible for the clinical and pathological changes which occur after the establishment of pneumothorax This is demonstrated clinically by evidences of diminished toxic absorption, namely, a fall in temperature, a reduced number of night sweats, and a rise in the opsonic index (Pigger) It would seem more consistent to ascribe this to a retarded lymph circulation than to an altered blood distribution Pathologically it may be argued that the atelectasis following pneumothorax restricting the lymph circulation further limits the spread of bacteria and favors the growth of connective tissue (Beneke) It would seem that lung compression might favor the escape of foreign infectious material into the lymph circulation, but the experiments of Graetz are evidence to the contrary, inasmuch as he has been unable to find artificially introduced material in the neighboring lymph-nodes

INDICATIONS FOR TREATMENT

It is obvious that the chances of symptomatic relief and the probability of ultimate cure by this pneumothorax therapy are dependent largely on one factor, namely the extent to which existing adhesions may permit retraction and compression of the lung The lung collapse will occur in proportion to the extent of the pneumothorax, the degree of pneumothorax will correspond to available pleural space, which in turn is dependent on the extent and firmness of adhesions

introduced nitrogen not only follows the periphery but occupies the space between the diaphragm and the lower lobe If adhesions are not present between the latter surfaces a pneumothorax of considerable extent is established and the lung retracts to the adherent areas of the upper thorax It *is in this last group of cases that the greatest* benefit in treatment may be expected

It should be emphasized, however, that in advanced cases with apparent involvement of the entire lung it is sometimes possible to create an extensive pneumothorax As a rule, however, the capacity of the pleural space is limited in such cases at the first injection In Cases 9 and 10 it was surprising to find that at a second injection at the same point a considerably greater amount of gas could be introduced under the same pressure before evidences of tension on pleural adhesions manifested themselves The explanation of this is that the previously existing adhesions must have become either stretched or separated It is probable that this occurs during subsequent attacks of coughing It is a physiological fact that during forced expiration the normal negative intrathoracic pressure becomes positive The pressure of an artificial pneumothorax is positive or slightly negative at inspiration and positive at expiration, the degree depending on the hydrostatic pressure exerted on the gas at the moment when its flow ceases During subsequent coughing, at forced expiration the pressure of this localized pneumothorax is raised to a higher level than that pressure at which it was introduced This explains the further separation of the pleural layers, which permits the introduction of a larger quantity of gas at the second injection It is obvious, therefore, that if nitrogen ceases to flow under a moderate pressure, raising this pressure to force its entrance is a dangerous procedure, for the subsequent rise in pressure concurrent on coughing may exert an undue tension on adhesions sufficient to rupture lung tissue when such adhesions are tough and unyielding

Inasmuch as adhesions are generally least prevalent in the earlier stages of phthisis, it might be argued that the first-stage cases are most amenable to this treatment The fact that pneumothorax *can* be easily esablished in such cases is by no means a proof that it *should* be Such patients are ordinarily cured by methods of hygiene, and there is no reason to believe that pneumothorax therapy should be substituted when suitable institution or home treatment can be carried out *If such means* are not at hand in a given case the pneumothorax treatment may be indicated

Pneumothorax therapy is especially indicated in that group of cases advanced beyond the promise of relief by methods of hygiene It is important to recognize this intervening stage before the disease advances to a point at which pneumothorax treatment is undoubtedly attended with

less promise Under the present status of the treatment of phthisis when hygienic methods prove unsuccessful, it is not uncommon to abandon hope of arresting the disease and to confine the treatment to symptomatic relief

Our group of cases consists with few exceptions of so-called hopeless cases Despite the symptomatic relief obtained in all of them permanent relief was obtained in but a small proportion In selecting material for this treatment a distinction should be made between those cases which are evidently not responding to hygienic treatment and are then regarded as hopeless, and those very advanced cases which are rapidly approaching their termination In the former group the patients should be treated with pneumothorax, the latter also perhaps for symptomatic relief but not with the hope of arresting the disease

The earlier writers on this subject, including Forlanini regarded all bilateral cases as hopeless for compression therapy The present opinion however, is almost universal that such cases should not necessarily be excluded The extent and activity of the process in the opposite lung must of course be the determining factor If an old process in the opposite side is quiescent there is no contra-indication Our results corroborate the statements of Brauer Forlanini, Schmidt and Lexer to the effect that a beginning process in the opposite lung is arrested in its activity by the immobilization of the lung most extensively involved With four exceptions our cases have presented bilateral involvement sometimes however with an inactive process on the side least involved

It is difficult to explain the apparent effect of a one-sided pneumothorax on the disease of the opposite lung This problem presents the conflicting theories of mobilization and immobilization the former represented by Freund's rib-dividing operation to mobilize a threatened or infected apex the latter supported by the artificial pneumothorax therapy and the extensive rib-resections resulting in immobilization

It is evident that the restriction of respiration of one lung resulting from pneumothorax provokes additional work by the opposite lung While immobilization of the lower parts of the lung seems to restrict the disease mobilization of the apex at the early stages tends also to check the disease If however the process of the untreated side is more extensive affecting the more mobile parts of the lung there is no question that its compensatory activity favors the spread of the disease

The commonly accepted theory is that the improved general condition and increased resistance of the patient relieved of toxemia by the pneumothorax therapy enable him to combat the beginning [illegible] of the opposite side

Certainly the [illegible]
results but many [illegible]
[illegible] of 102

own group were strictly of unilateral involvement, and yet the progress of six cases is most promising

SYMPTOMATIC RELIEF

Although the amount of autopsy material is insufficient from which to draw final conclusions as to the pathological changes resulting from artificial pneumothorax, the symptomatic relief attendant on the treatment is unquestionable This relief of symptoms is entirely in accordance with the pathological changes which appear to exist The most conspicuous benefit is apparently derived from diminished toxic absorption, not only from the toxins of tuberculosis but from those resulting from the mixed infection present in phthisical cavities A lowering of temperature is apparent in those cases which have been attended with fever, especially when a considerable amount of gas has been introduced This fall in

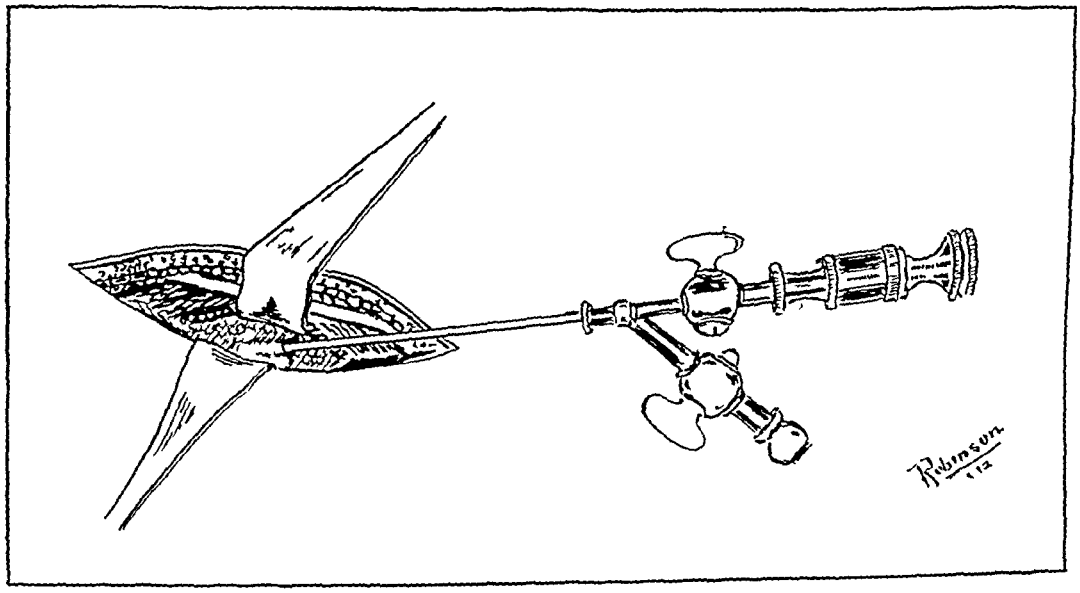

Fig 1.—Incision method of nitrogen injection Transparent parietal pleura exposed showing non adherent lung beneath it Needle inserted at oblique angle to avoid lung injury

temperature sometimes of immediate occurrence after the first injection may be temporary and followed by return of fever Subsequent injections tend to lower the temperature at the time and eventually it may remain permanently normal Coincident with lowered temperature there has often been a marked drop in pulse-rate with improvement in volume which has persisted A diminution in the frequency and severity of night sweats is not infrequently noted An improvement of the general condition of the patient with increased appetite and gain in weight is undoubtedly further proof of the reduced toxemia

A diminution in the quantity of sputum has been the most conspicuous element Though perhaps increased for the first twenty-four hours after the introduction of pneumothorax, which doubtless results from

partial evacuation of cavities under lung compression there is a subsequent falling off in the twenty-four hour amount The evidence of pus has also decreased and the odor in some cases been less troublesome In addition to the diminution in sputum quantity it is often noticeable that the total number of tubercle bacilli in a given microscopic field is reduced

Hemoptysis has rarely been present in the cases of our group and then it has been of slight degree In two of these the blood promptly disappeared from the sputum and has not since recurred In a third case which has come to our notice, where this symptom was causing considerable anxiety the first injection of nitrogen entirely arrested the bleeding

The relief in coughing has been interesting and inexplicable Several patients have voluntarily described soon after the first treatment increased ease in raising the collected sputum In some instances this was due perhaps to the primary increase in the quantity of sputum, its expulsion being favored by the distal compression A later alleviation of coughing has been noticeable in certain instances partly due to the reduction in the quantity of sputum to be raised, and furthermore, apparently as a result of reduced reflex irritation Occasionally however, while expectoration has diminished the cough has increased or remained unchanged

After continued treatment for varying lengths of time and a steady improvement in their general condition, certain patients have been enabled to return to work, encouraged not only by increased strength but by the limited coughing and spitting which had hitherto rendered them obnoxious to others

CHANGES IN CLINICAL FINDINGS

Physical examination reveals changes varying according to the previously existing conditions and to the extent of the pneumothorax established Numerous fine pleuritic râles may be heard at the periphery of the lung which entirely disappear over the area of pneumothorax Although this change may be partly due to the fact that such râles are rendered inaudible by the artificially reduced air-space between the chest wall and the lung we are nevertheless persuaded not only that the pleuritic râles disappear as a result of the separation of the pleural layers but that the intrapulmonary râles are obliterated or diminished as a result of the lung immobilization and the compression of the alveoli

Other changes in breathing and in the nature of râles occur which might be expected from the changes in the shape and mobility of certain portions of the lung and in the size and contents of the smaller bronchioles resulting from the established pneumothorax

We have frequently noticed where, previous to operation, the less involved lung had shown evidence of consolidation at the apex with clear bronchial breathing, that subsequent to the nitrogen injection this form

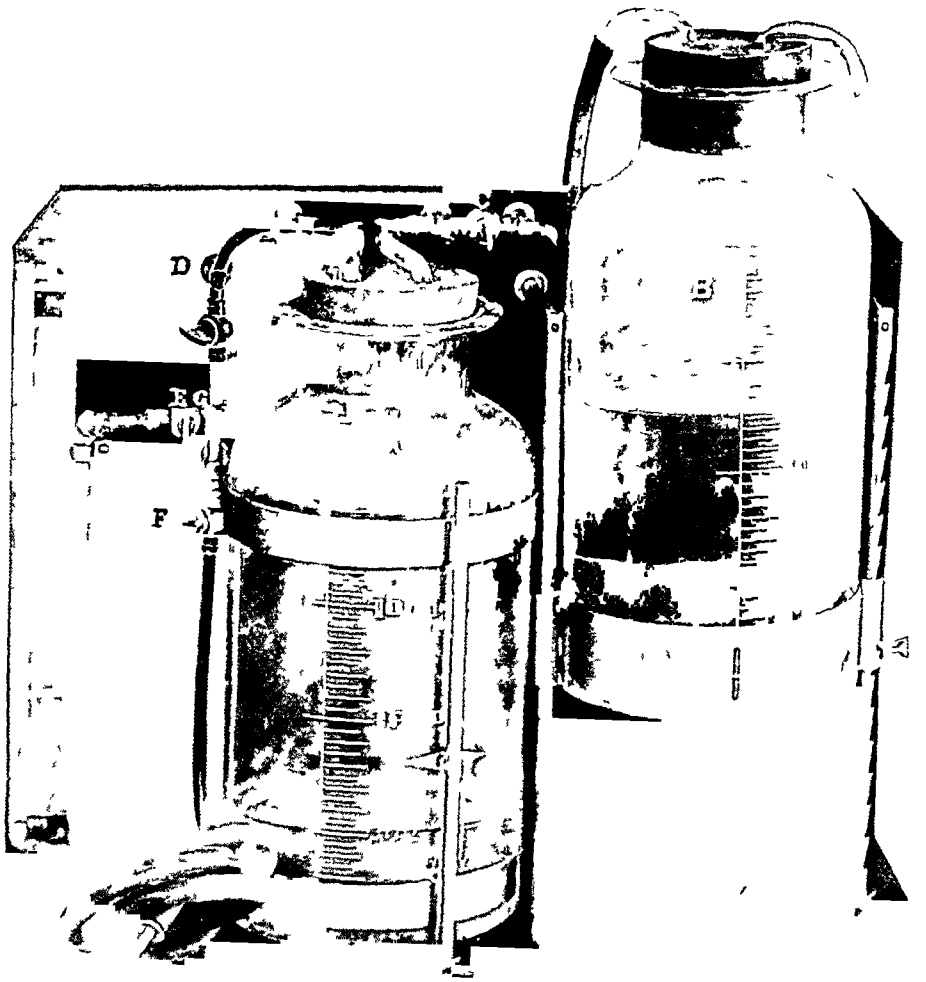

Fig 2.—Robinson's artificial pneumothorax apparatus

of breathing became altered to the bronchovesicular type Furthermore, the dulness to percussion and the resistance were less marked, and the breathing throughout the remainder of the lung took on a harsh and exaggerated character The explanation of this change of signs would seem to be that as the second lung is forced to take up a portion of the work of the first, it increases in size and those alveoli which have shown imperfect expansion previously are extended to their utmost capacity In the area of consolidation where tuberculous breathing had been the pre-

dominant characteristic the expansion of hitherto atelectatic vesicles modified the respiratory note showing clinically what is often found at autopsy that the extension of a tuberculous process is irregular rather than *en masse* Not only have there been definite changes in those physical signs denoting consolidation but as we have stated before there has been evidence of marked diminution in pulmonary moisture

With the subsidence of the symptoms of toxemia as a result of lung immobilization the opportunities for the use of tuberculin and other bacterial products may be more favorable More perfect drainage of cavities greatly aids all efforts to control any secondary infection that might be present and with it the accompanying lung destruction The cutting off of auto-intoxication with the fall in the temperature and pulse-rate gives a chance for effort to increase the general body resistance with various tuberculin products with advantage While these results are almost invariably the rule the encysting of pus in centers by too rapid compression may give rise to many unfortunate symptoms

In certain cases after considerable lung retraction under pressure some observers especially Brauer have noted a small pleural effusion in the compressed side This is demonstrable to a certain extent by physical signs but more surely by x-ray examination Fluid has appeared in small amounts in one or two of our cases generally about forty-eight hours after a large injection of nitrogen, but has not persisted for any length of time The amount has at no time been over 300 to 500 c c This condition may be due to pleural irritation from the nitrogen or possibly as a result of the derangement of pleural lymph circulation from the rapid retraction of the lung It is of no clinical importance and never increased to any considerable amount

adherence of the lung to the anterior chest wall with diminished dulness or tympany posteriorly, the scapular line should be selected

In other words, there are no rules governing the selection of the point of injection other than to choose that area most probably free of adhesions If it is presumed that the lung is free over a large area, that portion of the chest wall should be selected which is least covered with muscle tissue

In the absence of contra-indications the anterior chest in the nipple line on the right, or the anterior axillary line on the left are to be preferred

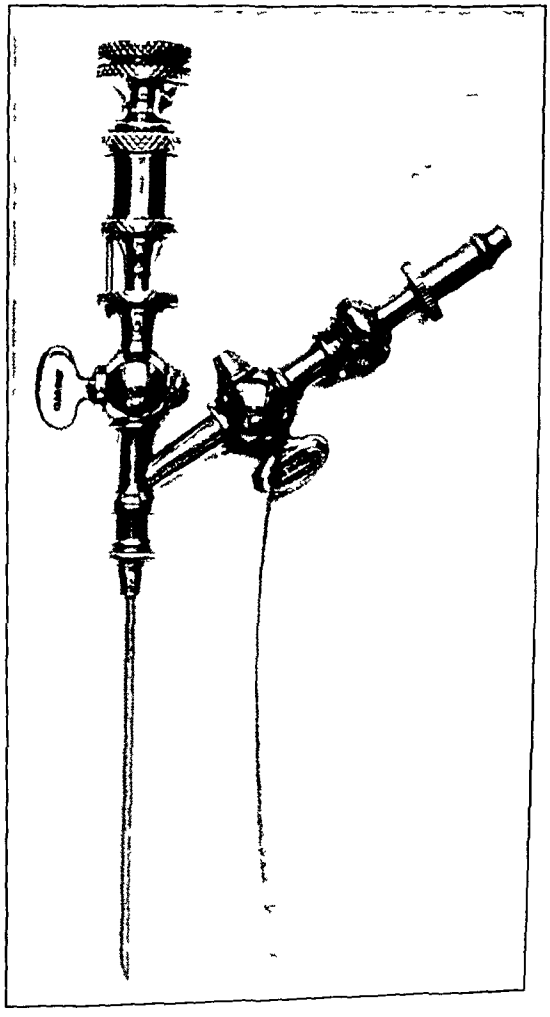

Fig 3.—Floyd's needle for nitrogen injection

THORACOTOMY OR THORACENTESIS

A difference of opinion has existed as to the method of introducing the hollow needle at the first injection The usual technic of thoracentesis is employed by Forlanini and, with a modification, by Schmidt The so-called Murphy-Brauer method is one of thoracotomy A 2 5 cm incision is made in the skin and underlying muscle and fascia layers exposing

the parietal pleura A blunt needle is then introduced through the exposed pleura

This incision method (Fig 1) is employed of course only at the first injection, the established pneumothorax preventing lung injury at the subsequent injections This inspection of the parietal pleura at the base of an incision has indeed been most assuring in those cases in which we have employed Brauer's method A transparent pleura with the lung surface moving to and fro beneath it exposes a field through which lung injury is quite impossible The blunt needle is then inserted at an oblique angle with the parietal pleura, the point sliding between the two pleural surfaces If a thickened opaque pleura on the contrary is discovered at a point where least expected, the needle may be inserted with great care for a distance of one-eighth of an inch, the syringe or manometer test (to be referred to later) being then applied before any attempt to introduce the nitrogen is made Rarely a non-adherent lung may be present beneath a thickened tuberculous pleura and the pleural space found and filled with nitrogen This is of such rare occurrence, however, that when by Brauer's method a thickened pleura is exposed it is preferable to close the first incision and make another over a new area

The point in dispute is whether the danger of injury to the lung is sufficiently great by the blind-puncture method to justify the operative method of incision and exposure of the pleura

The only fatalities attributable to the pneumothorax therapy have resulted from the needle puncture of the lung with subsequent injection of gas into a pulmonary vessel One case of hemiplegia and two of air embolism have resulted from this accident namely, three fatalities in a series of some 500 cases reported

It may be concluded therefore that avoidance of lung injury renders the treatment a safe one Forlanini argues that one accustomed to thoracentesis should with some experience be able to recognize that point at which the needle passes the parietal pleura He cautions however against the introduction of nitrogen until further proof has been established that

be extraordinary if accidents did not occur if a number of operators untrained in Forlanini's technic should undertake the free administration of this treatment with no more care than is expended in the common thoracentesis for pus or fluid A faithful observance of certain methods of determining the position of the needle-point referred to below is essential to avoid accident, and if one is not sufficiently painstaking to observe these rules one should employ the safer and more reliable incision method

Granting that the thoracentesis method is safe when correctly employed, there are certain features distinctly in its favor

The words "operation" and "cutting" employed in explaining to a patient the Murphy-Brauer technic are often sufficient to discourage him from submitting to treatment Many suitable cases were sacrificed for this reason when we were employing the incision method Patients responded far more willingly when it was explained that a needle-prick was the extent of the treatment

The Brauer operation, though a trifling one, is a time-consuming method Aseptic technic is essential and cannot be readily observed under unfavorable surroundings

Emphysema is of rare occurrence by the Forlanini method because the opening in the parietal pleura is promptly closed by the overlying tissues

In at least 60 per cent of our cases with incisions a greater or less extent of emphysema ensued This rarely caused discomfort, but indicated the escape of part of the contained gas, and when extensive seemed to interfere with the first intention healing of the incision By the operative method the intercostal muscles are sutured over the needle perforation of the pleura Until these two surfaces have become adherent leakage may occur resulting in emphysema as high as the neck and face Emphysema is of rare occurrence by the Forlanini method, and surgical asepsis and after-dressing are obviated

Being familiar with both methods, we are of the opinion that the Brauer technic at least presents the preferable method for the beginner He may at least witness in the incision what he must perform blindly in the thoracentesis method He will further discover how exact must be the position of the eye of the needle in the blind method to permit the introduction of nitrogen at the first injection It must be remembered that the aspiration of fluid from the chest is quite a different performance from the introduction of a gas In the former the pleural layers are already separated and the needle aspiration may be positive almost regardless of the depth of its introduction At the introduction of gas, however, a pleural space is not entered, but on the other hand the capillarity produced between the pleural layers keeps them in close contact, and the orifice of the needle must be inserted to exactly this point or the intrapleural pressure cannot be recorded, nor can the nitrogen be introduced

Undoubtedly the entering needle with its trocar not infrequently pushes the lung from the chest wall, thus separating the pleural layers for a short distance If, however, the needle is sharp or introduced by the stabbing method it is more likely to puncture the lung than to force a pleural space

ANESTHESIA

Whether the thoracotomy of Brauer or the thoracentesis of Forlanini is employed, local anesthesia is of paramount importance Cocain, even in weak solution, should not be employed in the incision method, at least not without the addition of epinephrin In six of the earlier cases of this group toxic symptoms developed from the use of cocain alone Though harmless in extent the disturbance was sufficient temporarily to interrupt the procedure, and became a troublesome complication A solution of 1 per cent novocain with 1 to 10 000 adrenalin has proved a desirable substitute in the later cases No symptoms have occurred with its use In the incision method the novocain is injected as in any local-anesthesia operation, the layers of the chest wall being anesthetized in succession The edematous infiltration of the muscle layers renders their distinction more difficult, but the rib borders serve as a landmark to the external intercostal layers and the change in direction of fibers distinguishes the internal intercostals Trauma to the parietal pleura is painful and care should be taken not to touch the latter in the process of dividing the internal intercostals A small compress soaked in novocain is then applied with pressure to the parietal pleura for thirty seconds which is sufficient to render it anesthetic The subsequent introduction of the needle is then accomplished without pain

Novocain should also be employed in the puncture method, although Forlanini does not refer to the use of anesthesia Robinson has emphasized the importance of anesthesia in all forms of thoracentesis arguing that when the latter is performed for exploration, the stabbing method often produces pain which prejudices the patient against subsequent punctures in case the first is negative, and also discourages the operator's persistence to continue exploration until pus is found In thoracentesis for nitrogen injection it is likewise important not to cause pain The essential feature of the treatment consists in repeated injections with gas from time to time If the patient suffers at the first injection he may not be persuaded to undergo the subsequent ones; moreover by reason of his experience he may discourage other members of the same clinic

tissues ahead of the needle may be well anesthetized before it is advanced Care should be taken that this interval is observed when it is expected that the next advance of the needle will perforate the pleura

A further important argument in favor of anesthetic thoracentesis in this treatment is that the subsequent introduction of the nitrogen needle through the anesthetized channel made by the hypodermic may be performed slowly and carefully A minute skin incision with a narrow double-bladed pointed knife enables the operator to introduce the nitrogen needle without any marked obstruction One may under these conditions note the slight resistance of fascia layers followed by the lack of resistance of the intercostal muscle tissues, warning him that the needle point is approaching the parietal pleura The resistance of the pleura, even when not thickened, is then distinguishable, and the sudden ease of advancing the needle beyond indicates to the operator that the pleural cavity is entered and that further advance endangers the lung At this point he employs a method described below of proving further that the opening of the needle is between the pleural layers

Anesthetic thoracentesis also enables one to avoid the under surface of the rib above, thus diminishing the possibility of injury to the intercostal vessels

The usual stabbing method of thoracentesis is then distinctly to be avoided in this treatment because of physical and esthetic injury to the patient and because of the added danger of lung injury from the lack of absolute control of the depth of introduction

TO CONFIRM THE CORRECT DEPTH OF THE NEEDLE-POINT

If the incision method of Brauer has been employed and the parietal pleura is found to be transparent and non-adherent, the needle may be slipped in between the pleural layers and the nitrogen injected without further delay If on the contrary the direct thoracentesis method has been substituted, one must have ample evidence before introducing the nitrogen that the eye of the needle is between the pleural layers Forlanini's method of attaching a syringe to the butt of the needle is perhaps a less complete precaution than the use of a manometer

Brauer has always employed a manometer as guide in the introduction of the needle, and we are convinced that it is not only an essential feature of the apparatus, but also the surest and simplest means of avoiding risk

When the needle has been inserted to what digital sense would indicate to be the correct depth, the trocar is removed, and the needle-cock closed The rubber tubing leading from the apparatus is supplied with a beveled metal tip which forms a tight joint when inserted into the base of the needle Before making this connection the apparatus cocks are so arranged that the manometer is isolated from the nitrogen circuit After

connecting the tubing with the needle the needle-cock is opened If the operator has been fortunate enough to insert the needle to the correct depth the negative intrathoracic pressure is recorded by the manometer, and inasmuch as this negative pressure varies at inspiration and expiration, an oscillation of the water-column is visible and coincident with the respiratory movements If the needle-point is partly obstructed by contact with adhesions or lung tissue, this oscillation may not be more than 0 5 cm Such a trifling oscillation is also found when the pleural space entered is one of small capacity on account of neighboring adhesions, but whether this oscillation be a complete or restricted one, its presence is an unerring guide that nitrogen may then be safely introduced If the oscillation has been small, the amount of nitrogen injected is correspondingly low A free oscillation of from 3 to 4 cm is evidence of greater lung mobility and the extent of the pneumothorax produced is correspondingly greater On two occasions we have risked the connection of the nitrogen pressure in spite of the lack of this manometer reading A slow nitrogen flow in one instance followed, and after introduction of 50 c c the cocks were again adjusted to connect with the manometer To our surprise a respiratory oscillation was then manifest The explanation of this occurrence rests in the fact that the gas entering under slight pressure forced from the eye of the needle whatever may have previously been in contact with it, presumably the visceral pleura Despite the success of this adventure its danger was unquestionable, a direct introduction of nitrogen into a vein being one of the alternatives which might have occurred This is an unnecessary and unwarranted risk A slight movement of the needle either inward or outward will bring the needle opening to the desired point with resulting oscillation of the manometer, unless adhesions are present If these painstaking changes in the position of the needle do not result in a positive manometer reading, even when the patient is requested to perform deep breathing, ample proof is present that a pleural space and pneumothorax cannot be established at this point, and the needle should be withdrawn and another area selected

NITROGEN PRESSURE

Having obtained the desired respiratory oscillation of the manometer; the apparatus cocks are so adjusted that the manometer circuit is cut out and the nitrogen gas may then enter the needle If the displacement of nitrogen in the reservoir occurs rapidly it is advisable partially to close the needle-cock in order that the pneumothorax and retraction of the lung may not occur too suddenly

It will be noted in the case reports that the nitrogen pressure employed has not been expressed in manometer readings The pressure employed has been varied at will according to the conditions present Time was not taken at each of these alterations to arrange the cocks to

connect with the manometer A pressure of 12 cm of water was in no case exceeded If nitrogen will not flow under this pressure the undertaking may be abandoned even though a respiratory excursion of the manometer is previously obtained Under favorable conditions the nitrogen gas will enter at the rate of 50 c c per minute under a pressure of from 6 to 10 cm of water A more rapid flow and a higher pressure means economy of time but a patient reacts less to the altered conditions within the thorax if they occur gradually

Not infrequently, even though the needle be properly adjusted as proved by the manometer oscillations, the nitrogen will flow more slowly Increasing the pressure under these conditions will generally accelerate the flow We regard this phenomenon as evidence that the pleural space entered is one limited by adhesions and that the subsequent pneumothorax will be a slight one In three cases it has happened that as many as 1,000 c c of nitrogen have been injected with this increase in pressure, and in these instances it would seem that the pleural space was not restricted but that the opening in the needle may have been partially obstructed

QUANTITY OF NITROGEN

Witnesses of the treatment invariably inquire how much nitrogen should be injected at each sitting There is no answer to this question, since the amount of nitrogen injected will always depend within certain limits on the conditions found in a given case If the nitrogen flow under *moderate pressure is apparently unrestricted* 600 to 800 or even 1,000 c c may be injected at the first operation Forlanini habitually employs a moderate injection at first Though inclined to adopt this technic in our earlier cases we are convinced that at least 600 c c are frequently well tolerated and that the relief of symptoms so necessary for the encouragement of the patient is more marked if the first injection is a generous one

In those cases apparently free of adhesions 600 to 1,000 c c may be introduced at the first injection without the least discomfort, the respirations are slightly increased and the patient is aware of an altered condition in the chest The pain may not even be suggested One thousand cubic centimeters should be the limit of injection at the first sitting, even in the absence of symptoms

If, on the contrary physical signs, difficulty in adjusting the needle-point, and slight respiratory oscillation of the manometer and retarded nitrogen flow indicate that probability of a limited degree of pneumothorax, one should be guided by the degree of discomfort to the patient Generally in such cases the entrance of the nitrogen, despite a gradual increase in pressure becomes steadily retarded Concurrent with this diminution in flow is some indication of distress The patient describes a full or tense feeling in the chest, generally at once relieved by tempo-

rarily checking the flow On renewing it the symptom recurs and may later result in a distinct pain which is identical with the ordinary pleurisy pain This is generally noted in the lower chest anteriorly in the region of the diaphragm The small area of pneumothorax established in such cases is often limited below by adhesion between the lower lobe and the diaphragm Tension of this adhesion on the diaphragm is subjectively expressed by pain If, on the contrary, the diaphragmatic surface is clear, the process being confined to the upper lobe, a greater amount of nitrogen can be injected and pain does not develop The onset of distress and the first sign of pain should be accepted as sufficient reason for removing the needle, not only at the first injection but in subsequent ones Whatever actual pain occurs is bound to increase if the flow is continued, and furthermore even when the treatment is promptly suspended whatever pleurisy pain exists at the time will continue for at least three to four hours

Ordinarily a larger pneumothorax may be established at the second and third injections than at the first If the pleural space seems comparatively unrestricted, 1 200 to 1 800 c c may be injected If in the restricted cases symptoms have occurred after the introduction of a limited quantity (200 to 400 c c) it is not uncommon to find that even 600 to 800 c c may be tolerated at the second and third injections without the recurrence of the same symptoms This phenomenon is explained in a previous paragraph The amount of the previous injection therefore should be regarded as a guide but not as a restricted limit to the amount of later injections

FREQUENCY OF TREATMENTS

It would seem that the tendency of the lung to reexpand is gradually reduced as time elapses Nitrogen furthermore is apparently more rapidly absorbed in certain patients than in others and any dilution of the gas either in its manufacture or in its introduction will of course hasten its absorption

Concerning the frequency of treatments again no rule can be established Generally speaking, the patients with restricted pleural space in whom the first treatment results in a limited pneumothorax should be treated again within a week, the frequency of subsequent injections depending on whether the quantity of nitrogen tolerated gradually increases If a first treatment indicates that a considerable pneumothorax can be established two or three weeks may be allowed to intervene before a second treatment The symptoms of the patient and the size of the tympanitic area representing the pneumothorax are contributory evidence as to the permissible interval between injections In cases in which 800 to 1 200 c c have been introduced at the third injection a month or six weeks may be allowed to intervene between the later ones

APPARATUS

Figure 2, showing Robinson's apparatus, illustrates the principles employed in all forms of apparatus Two bottles of 3,500 c c capacity are employed One is stationary and filled with water containing 2 drams of pyrogallic acid to take up any oxygen which may enter in conjunction with nitrogen. Nitrogen gas is then forced into the stationary bottle (A) displacing the water back to bottle B At completion of this displacement the apparatus is ready for use On opening certain cocks the water in bottle B replaces the nitrogen in bottle A, gradually filling it The difference in the water levels of the two bottles represents the pressure under which the nitrogen is injected, the rapidity of its injection being regulated by the size of the opening in any one of the cocks When bottle B is full the maximum pressure is obtained amounting to about 14 c c of water As the water levels approach one another bottle B may be raised as in Figure 2, thus maintaining the pressure until most of the nitrogen has been displaced, when the pressure is necessarily reduced With this hydrostatic mechanism the pressure may be varied at will, never attaining the dangerous limit

The arrangement of cocks *d*, *e*, and *f*, corresponds to the substitution of a three-way cock at point *g* In other words with cock *d* closed and *e* and *f* open, a direct connection is established between the thoracic cavity and the manometer With cock *f* closed and *c*, *d*, and *e* open, connection is made between the confined nitrogen and the manometer, thus recording the pressure represented by the difference in water levels of bottles A and B With cock *e* closed and all others open the nitrogen passes directly from bottle A into the pleural cavity

This apparatus has the advantages of stability and portability The fixation of all cocks and tubing to the backboard facilitates their opening and closure, while the use of rubber tubing with clips such as we employed in earlier apparatus proved a constant source of annoyance

Figure 3 illustrates a needle which Floyd has designed for use in pneumothorax therapy It is of the type of Brauer's needle, with, however, several changes in construction which our experience has demonstrated to be of value

REPORT OF CASES

CASE 1.—*Patient*.—B M, a waitress, aged 28 Past history unimportant Well until a few weeks ago when following a cold she developed a cough, expectoration, and night sweats Some loss of weight

Examination.—Fairly well developed and nourished Heart not remarkable Lungs Well-marked area of consolidation over the right upper lobe with evidences of consolidation throughout the right back with cavity formation in lower lobe Numerous râles On left side over upper lobe consolidation with moisture

First Operation.—Sept 6, 1909 Patient taken to Massachusetts General Hospital for artificial pneumothorax operation Under cocain, incision made in left intercostal space on right below inferior angle of scapula, and carried down

to pleura through which exposed lung could be seen Small opening made in pleura through which needle was introduced and 700 c c of nitrogen injected Wound then sutured

Postoperative Condition—Some emphysema developed afterward Following operation some dyspnea Examination showed tympanitic note over lower lobe on right extending well up into the vault of axilla Fremitus absent Râles in this region have disappeared Heart pushed somewhat to left Sept 16, 1909 Expectoration has diminished General condition good Tympanitic note over right lower lobe persists with very distant breathing and slight tactile fremitus

Second Operation—Sept 27, 1909 In region of first operation, 700 c c of nitrogen were injected into pleural cavity through needle Pulmonary signs about as before

Subsequent History—Patient followed from October, 1909, to July 13, 1910 At intervals of a few weeks, injections of nitrogen were given, the largest single injection being 900 c c, with the result of improving the condition of the patient, diminishing the amount of sputum and causing some gain in weight Toward the end of this time examination of the lungs showed a practical absence of moisture on the left side and very little activity on the right About July 13, 1910, without warning, patient had a severe hemorrhage and died in a short time

This was a case of rapidly progressing disease which was advanced when taken under treatment, and was much retarded in its progress as the result of nitrogen injections

CASE 2—*Patient*—L H S, female, aged 29, shoe inspector Family history and previous personal history unimportant About two years ago patient began to be troubled with cough and expectoration, which have persisted ever since There has been a marked loss of weight, and in the early part of the illness a hemorrhage of one pint

Examination—Sept 16, 1909 The patient has an advanced case of phthisis involving on the left the upper lobe and all three lobes on the right Sputum is positive, twenty-four-hour amount being from 2 to 7 drams

Operation—Patient was operated on September 16 under cocain in the seventh left intercostal space, in the region of the angle of the scapula Incision was made down to the pleura, which was then entered by a small needle, but no free space could be found after considerable manipulation Wound was then closed and a second area selected in the fifth intercostal space, anterior axillary line Again, following an incision down to the pleura, needle was carried through it, but no pleural space was found in this region The wound was then closed

This case was entirely unfavorable for treatment with artificial pneumothorax on account of obliteration of the pleural cavity

CASE 3—*Patient*—J J S, salesman, aged 30 Two cases of tuberculosis in immediate family Personal history negative For five months patient has had a persistent cough, with considerable expectoration and occasional night sweats During this time has lost 12 pounds in weight

Examination—Sept 8, 1909 A man in fair general condition Heart negative Lungs On the left side there is consolidation with cavity formation at the apex with evidences of moisture throughout the upper two-thirds of the back On the right the upper two lobes are extensively involved with cavity formation in front below the clavicle

Operation—At this date the patient was operated on under cocain in the right eighth intercostal space near the angle of the scapula Eight hundred c c of nitrogen were injected, causing considerable pain, pleural in type

Postoperative Condition—Examination following the operation showed an increased harshness of respiratory murmur on the left side in the right back rales were much fewer, dulness and resistance had disappeared below the level of the midscapula and tactile fremitus was almost absent Following operation

patient had considerable pain and raised a large amount of sputum in the next two days Examination one week after operation showed a well-marked area of tympany over the lower two lobes on the right and very little moisture on the left

Subsequent History—Patient was followed for a year and a half, being given a number of injections of nitrogen in the same area by means of the Brauer needle, the amount of nitrogen being steadily increased to about 1,000 c c at one time Following each injection there was some increase of symptoms, probably as the result of the effect of pressure on the lung cavity At the end of six months' treatment the process in the chest was brought to a standstill The case, however, was a far advanced one from the beginning, and reports at the end of a year and a half show the patient again to be losing ground

CASE 4—*Patient*—H C, male, aged 20, stone cutter Family and personal history negative For one year there has been constant cough with steadily increasing expectoration, frequent night sweats and considerable loss of weight

Examination—Sept 22, 1909 Poorly developed and nourished Chest narrow On left, upper lobe shows marked evidences of consolidation with a few dry râles Signs of cavity at left apex On right, above the third rib in front and throughout the back there is evidence of consolidation with numerous râles and cavity formation at the right apex in front Dextrocardia present

Operation—At the date already given, in the anterior axillary line on the right at about the fifth intercostal space, an incision was made under cocain down to the pleura Nitrogen gas was allowed to enter the pleural cavity through a needle until 800 c c had been injected The wound was then closed

Postoperative Condition—Examination following the operation showed the heart to have moved toward the left The respiratory note on the left side changed from bronchial to bronchovesicular and was less intense, and the râles had disappeared On the right, signs of cavity had disappeared, râles were much fewer, and below the third rib there was marked tympany

Subsequent History—A week following the operation a second injection of nitrogen was performed of about 400 c c in amount The patient then returned home and refused to report for a subsequent treatment He died three months later

CASE 5—*Patient*—A M, male, aged 36, plasterer Family and personal history negative Present illness began with cough and hemorrhage about four weeks previous to Oct 8, 1909 Sputum is positive

Examination—Poorly developed and nourished Temperature normal, elevated pulse Heart somewhat enlarged Lungs On left side, consolidation with very little moisture involves upper lobe On the right, consolidation with marked activity over upper two lobes On Oct 22, 1909, for the last three days patient has been under observation in bed on account of constantly raising blood, from 2 to 6 ounces daily

Operation—Incision was made in the fourth interspace on the right in the axilla No pleural cavity could be demonstrated This wound was then closed and a second incision made in the nipple line in the fifth intercostal space Here 600 c c of nitrogen were readily given into the pleural cavity

Postoperative Condition—Following the operation examination showed the breathing on the left over the area of consolidation was much modified On the right, percussion showed a tympanitic note up to the second rib Evidences of moisture much diminished

Subsequent History—Patient was followed at an interval of a week or two until May 1, 1910 Following the operation there was entire cessation of pulmonary bleeding, with no return Nitrogen injections were given in the lower right chest at intervals of from three to four weeks the largest single amount being 1 400 c c Examination toward the end of the period of observation showed the left lung to be entirely dry There were slight evidences of moisture at the

extreme right apex, and a tympanitic note at the right base over the area of nitrogen injections On May 1, 1910, patient was doing well, his cough was very slight

In this case, although one of marked pulmonary tuberculosis, the disease has been arrested as the result of pulmonary compression Patient has been steadily at work since his first injection of nitrogen

CASE 6—*Patient*—E F, male, aged 21, shoe inspector Mother died of tuberculosis Personal history previous to present illness negative For about two years and a half patient has had a persistent cough which has been steadily increasing, accompanied by night sweats, temperature and loss of weight

Examination—Oct 9, 1909 Poorly developed and nourished Heart not remarkable Pulmonary consolidation is present in upper lobe on left and upper two lobes on right, with evidences of cavity at the right apex

Operation—An incision was made in the fourth intercostal space in the anterior axillary line on the right and carried down to pleura, which was found to be non adherent Nitrogen readily entered the cavity to the amount of 575 c c

Subsequent History—Following the injection dulness in the left lung was much less marked, breathing became less bronchial and more bronchovesicular, fewer râles were present Nitrogen was found to have invaded the anterior pleural space on the right, forcing the lung backward Patient was kept under observation for about a month, but on account of his poor general condition, continuation of the treatment was thought inadvisable, especially as little collapse of the lung could be obtained on account of extensive adhesions posteriorly on the right

CASE 7—*Patient*—F G, male, aged 19, machinist Father died of tuberculosis two years ago Patient has been under treatment at various times at Rutland and Mattapan Day Camp his illness having begun with a hemorrhage in February, 1907 At the present time, October, 1909, he has a persistent cough, with considerable expectoration showing tubercle bacilli There has been considerable loss of weight

Examination—Fairly well developed and nourished Heart pulled toward the left axilla Lungs show consolidation on the right over the upper lobe Considerable moisture on the left, involving the upper two thirds of the lung, signs of cavity below the left clavicle

Operation—Oct 20, 1909 Patient operated on in the left fifth intercostal space anterior axillary line Incision carried down to the pleura, which was found to be non-adherent, and 500 c c of nitrogen were injected without symptoms

Subsequent History—Patient reported for observation for about eight months, and was given periodic injections of nitrogen at intervals of three or four weeks, the maximum amount injected at one time being 600 c c Under this treatment evidences of activity on the right entirely disappeared signs of cavity below the left clavicle became much less marked and sputum diminished somewhat in amount, there was also a temporary gain in weight After about eight months' observation, patient developed marked intestinal symptoms, which steadily increased in severity, and from which he died on July 1 1910 The effect of the treatment in this case would seem to have been a very marked retardation of the pulmonary process

CASE 8—*Patient*—A M, female aged 22 no occupation Family and personal history negative About eight months ago following a severe cold patient developed a persistent cough, which has steadily increased and been accompanied by considerable expectoration There has been a marked loss of weight and frequent night sweats

Examination—Nov 1, 1909 Fairly well developed and nourished Heart not remarkable Over the entire left lung evidences of consolidation especially in the upper lobe, with scattered râles throughout No activity on the right side

Operation—Nov 3, 1909 Incision over the fourth rib anterior axillary line on the left was carried down to the pleura This was found to be adherent to the lung, and the needle could not demonstrate any pleural cavity A similar incision was made over the seventh rib in the axillary line with like result This case proved unfavorable for treatment on account of obliteration of the pleural cavity

CASE 9—*Patient*—E A W, female, aged 39, engaged in housework Two brothers and two sisters died of tuberculosis Personal history negative Following a severe cold in March, 1909, patient developed a persistent cough and expectoration Examination some four months later showed her to be suffering with a marked case of pulmonary tuberculosis with positive sputum There has been considerable loss of weight

Examination—July 21, 1910 Fairly well developed and nourished Heart not remarkable Consolidation involving the right upper lobe and the upper two thirds of the lung on the left Marked activity on this side

Operation—The following day patient was operated on in the scapular line at the level of the eighth rib on the left side Incision was carried down to the pleura, through which the lung could be seen to move with respiration With some difficulty, on account of surrounding adhesions, 1,200 c c of nitrogen were injected, the gas extending down toward the diaphragm

Subsequent History—Patient remained under observation for eight months following the first operation She was given frequent injections of nitrogen at intervals of about one month, the largest single amount being 1,400 c c As a result of the treatment there was some gain in weight, considerable diminution in the amount of expectoration, and examination showed the process to have been arrested The right chest became entirely dry and there was very little moisture on the left side

CASE 10—*Patient*—M H W, female, aged 31, engaged in housework Two brothers and father died of tuberculosis Patient had pneumonia one year ago Present illness began following the attack of pneumonia, with cough and expectoration and some hemoptysis There was a loss of 24 pounds in two years

Examination—July 26, 1910 Fairly well developed and nourished Heart shows double mitral disease Examination of lungs shows upper half of left lung to be extensively involved On the right side the upper two lobes are markedly infiltrated, with considerable activity Patient six months pregnant

Operation—Three days later patient was operated on in left posterior axillary line Incision made through chest wall and carried down to the pleura Nitrogen readily entered the pleural cavity to the amount of 1,100 c c, following which the wound was sutured

Subsequent History—Patient under observation for eleven months She was given a few injections of nitrogen following the first operation

Postoperative Condition—Confinement interfered with systematic treatment, the largest amount at one time given being 1,300 c c Examination at the end of the period of observation showed her general condition to be good The process on the left side had become entirely quiescent, and the evidences of activity on the left were much diminished The patient had stood the confinement well

CASE 11—*Patient*—H F, school girl, aged 15 Family and personal history not important Six months previous to July 30, 1909, patient developed a severe cold followed by a cough, which has persisted, and three months ago raised some blood She has been under observation at a day camp for about four months and in spite of systematic treatment has steadily lost ground

Examination—Fairly well developed and nourished Heart not remarkable Upper two lobes on right show extensive involvement with considerable moisture Upper lobe on left shows a moderate amount of activity

Operation—About six weeks after examination patient was operated on by means of the Brauer method in the left anterior axillary line, and 1,200 c c of nitrogen were injected without difficulty

Postoperative Condition—Period of observation lasted for ten months, during which time the patient was systematically injected with nitrogen, the largest amount given at one time being 1,400 c c Examination on May 1, 1911, showed no activity on the right side and almost none on the left Sputum, however continued to be positive General condition is excellent In this case we feel that the treatment has brought the disease to a standstill, but on account of the age and lack of intelligence of the patient the ultimate outlook is poor

CASE 12—*Patient*—F J P school boy aged 15 Family and personal history negative On July 23, 1910 patient reported at the Boston Consumptives' Hospital giving a history of cough, expectoration and hemoptysis, having a duration of about four months Sputum was positive

Examination—Fairly well developed and nourished Heart shows mitral regurgitation Lungs On the right side the upper two lobes show extensive infiltration and activity Over the left upper lobe there are evidences of consolidation with slight activity

Operation—On Aug 3 1910, patient was operated on by means of the Brauer method directly beneath the right nipple The needle readily entered the pleural cavity and 1,200 c c of nitrogen were easily injected without symptoms

Subsequent History—Patient remained under observation for one year and was given monthly injections of nitrogen, the largest single amount being 1 400 c c As a result of the treatment there has been a marked gain in weight, cough has entirely disappeared and there is very little expectoration Examination shows an arrest of the pulmonary process

CASE 13—*Patient*—D J D, male aged 54 laborer Family and personal history negative Feb 17, 1908, patient reported for his first examination, having had some cough and expectoration Examination at this time showed him to be an incipient case, but even under treatment he has steadily lost ground

Examination—Aug 2, 1910 the left lung showed consolidation over the upper lobe without activity On the right side over the upper two lobes signs of consolidation with considerable activity

Operation—At this date patient was operated on beneath the right nipple by means of the incision method The parietal pleura was readily exposed and 1,200 c c of nitrogen entered the pleural cavity without symptoms

Subsequent History—Observation of this patient continued for five months, during which time there was considerable gain in weight Injections of nitrogen were continued for three months with some improvement of the pulmonary condition On account however, of poor surroundings and bad habits further treatment was thought undesirable and patient was sent into a hospital A temporary improvement in this case was noticeable, however

CASE 14—*Patient*—M K blacksmith, aged 39 Mother died of tuberculosis Personal history negative Patient reported at the Boston Consumptives' Hospital on Jan 21, 1910, giving a history of cough and expectoration with chest pain of about two months' duration He has since been under treatment at various institutions

Examination—Aug 16, 1910 Heart negative Lungs On the left side over the upper lobe there is consolidation and a moderate amount of activity On the right over the upper half of the chest there is evidence of consolidation and of considerable activity

Operation—Patient was operated on directly below the right nipple by means of the incision method and without difficulty 1 000 c c of nitrogen were injected into the pleural cavity As a result of the injection there were marked

evidences of pneumothorax over the right lower lobe behind, moisture on the right side was much diminished

Subsequent History—Patient was given frequent inoculations of nitrogen at intervals of from two to four weeks over a period of seven months At the end of this time there had been little or no improvement Symptoms had persisted Following bronchitis the process extended through the right lung Patient died March 25, 1911, with meningeal symptoms Autopsy was refused

CASE 15—*Patient*—M J K, female, aged 44, engaged in housework Family and personal history negative Patient has been under observation at the Boston Consumptives' Hospital since May 7, 1909 For the past eight months she has had persistent cough, with considerable expectoration, occasional chills and some night sweats There has been a loss of 18 pounds in weight

Examination—Aug 18, 1910 Well developed and nourished Heart enlarged Lungs Consolidation over the upper two lobes on the right side and the upper lobe on the left with considerable activity

Operation—Patient was operated on by means of the incision method in anterior axillary line on the right, and 1,300 c c of nitrogen were injected without symptoms

Subsequent History—There was some gain in weight and a diminution of the cough and expectoration following the first injection of nitrogen At the end of two weeks a second injection was attempted, but after causing the patient some pain further treatment was refused We have been unable to follow this case further

CASE 16—*Patient*—A E M, female, aged 25, engaged in housework Family and personal history negative At first examination (Aug 4, 1909) patient showed a well-marked case of pulmonary tuberculosis, with history of cough and expectoration of a year's duration

Examination—Aug 18, 1910 Well developed and nourished Heart not remarkable Upper two-thirds of left lung show evidences of consolidation with moderate amount of activity Upper lobe on right similarly involved

Operation—Aug 24, 1910 By means of the incision method in the fifth space anterior axillary line on the right, the pleura was exposed but found to be adherent and the wound was sutured A second area was selected in the scapular line in the ninth interspace This attempt also failed, as the visceral and parietal pleuræ were entirely adherent Pneumothorax treatment, therefore, had to be given up, as the case was unfavorable

CASE 17—*Patient*—R F C, seamstress, aged 22 Family and personal history negative For some months previous to Aug 25, 1910, patient has been under observation, having given a history of cough, expectoration and loss of weight

Examination—Poorly developed and nourished Heart somewhat enlarged, action poor Lungs show infiltration, involving the upper lobe on the right and the upper two thirds of the left lung There are evidences of cavity formation in the left front

Operation—By means of an incision through the intercostal muscles the pleura was exposed in the left eighth intercostal space, and 1 200 c c of nitrogen were readily injected A large amount of pus was expectorated immediately following the operation

Subsequent History—Patient continued under observation for about seven months and was given periodic injections of nitrogen at about three or four weeks' intervals Examination Jan 13 1910, showed no loss of weight during this period of observation There is less evidence of dulness in the right chest, breathing has been largely changed from bronchial to the bronchovesicular type in the area of infiltration On the left side there is evidence of collapse of the lower lobe The progress of the disease however has not been checked and the outlook is unfavorable

CASE 18.—*Patient*.—R. R., female, aged 26, engaged in housework. Family and personal history negative. For the past three weeks patient has had considerable cough and expectoration, has been gradually losing weight. Sputum is positive.

Examination.—Aug. 30, 1910. Well developed and nourished. Heart not remarkable. Lungs show consolidation on the right side over the upper lobe and on the left over the upper two thirds of the lung. Activity marked on the left side.

Operation.—Under novocain anesthesia an incision was made in the anterior axillary line at the level of the left nipple. Pleura was exposed, which was found to be white and thickened. The entrance of the needle, however, was unobstructed and 1,000 c.c. of nitrogen gas readily entered the pleural cavity. Following the operation, examination of the chest showed a fairly extensive area of pneumothorax localized in the lower left front of the chest, considerable diminution in the amount of moisture.

Subsequent History.—Two weeks after the operation patient unexpectedly moved out of town and efforts to find her have been entirely unsuccessful. Thus a very favorable case for this method of treatment was lost.

CASE 19.—*Patient*.—W. G. J., female, aged 23, engaged in housework. Personal and family history unimportant. For a year previous to Aug. 30, 1910, patient has had a constant cough and expectoration following a cold. There had been occasional night sweats but no hemoptysis.

Examination.—Fairly well developed and nourished. Heart not remarkable. Lung examination shows considerable involvement in the upper half of the right chest and the upper two thirds of the left with considerable moisture. There are evidences of cavity formation below the left clavicle.

Operation.—This case was considered a suitable one for pneumothorax treatment, and under novocain an incision was made in the anterior axillary line on the left side, at the level of the left nipple. Transparent pleura was readily exposed and the inserted needle found the pleural cavity without difficulty. Six hundred c.c. of nitrogen were easily injected without discomfort.

Subsequent History.—There was a rapid healing of the wound. Patient remained under observation for about seven months and was periodically injected with nitrogen, the largest amount given at one time being 1,300 c.c. Examination Jan. 20, 1911, showed a diminution in the amount of moisture on the left side with diminished evidences of cavity formation. Process on the left, however, was only temporarily checked, and the prognosis on May 1, 1911, is poor. One of the discouraging features in this case has been the weak heart action.

CASE 20.—*Patient*.—M. M., female, aged 19, employed in shoe factory. Father died of tuberculosis six years ago. Personal history unimportant. For about a year previous to Aug. 18, 1910, following a heavy cold, there has been a persistent cough with considerable expectoration and a marked loss in weight. Toward the beginning of illness patient had one small hemorrhage. Tubercle bacilli in sputum.

Examination.—Fairly well developed and nourished. Heart not remarkable. Upper two thirds of right chest show signs of infiltration and there are evidences of moisture throughout. There are signs of cavity formation in the upper left front and consolidation of the upper half of the left lung. Pneumothorax treatment was determined on in an effort to check this process.

Operation.—A point in the anterior axillary line on the left was selected five inches outside the nipple and by means of the incision method the pleura was exposed and 1,000 c.c. of nitrogen were injected without symptoms. As a result of the operation an area of tympany developed in the lower part of the left chest.

Subsequent History.—Observation was continued until May 1, 1911. During this time periodic injections of nitrogen by means of thoracentesis have been given, up to 1,300 c.c. in a single amount. As a result of the treatment the right lung is almost entirely free from moisture and only a few musical râles persist at the

left apex In this case the prognosis has been materially improved as the result of the treatment

CASE 21.—*Patient*.—A. C., female, aged 34, engaged in housework. Family and personal history negative. For about five years patient has complained of a constant cough, periodic night sweats and loss of weight and strength.

Examination.—March 14, 1911. Fairly well developed and nourished. Heart negative. Signs of consolidation over the upper lobe on the right side and upper two-thirds of the lung on the left.

Operation.—At the date given above, by means of thoracentesis, 400 c.c. of nitrogen were injected in the left pleural cavity in the anterior axillary line without discomfort.

Subsequent History.—This patient has been followed only three or four months. At the end of this time, as a result of injections of nitrogen every two or three weeks, there has been a steady diminution of cough and expectoration. There is less evidence of activity in the chest and there has been some gain in weight. On account of the short period of treatment the ultimate outcome cannot be surmised.

CASE 22.—*Patient*.—F. G., machinist, aged 36. Family and personal history negative. For three months previous to April 20, 1911, patient had been losing in strength and had a persistent cough. This has recently increased, accompanied by night sweats, fever and thoracic pain.

Examination.—Well developed and nourished. Heart not remarkable. Infiltration of the left lung over the upper half with considerable moisture and on the right side above the level of the second rib in front.

Operation.—By means of thoracentesis 400 c.c. of nitrogen were injected in the anterior axillary line on the left side.

Subsequent History.—This patient has now been followed for two months and has been given frequent injections of nitrogen, the largest amount at one time being 800 c.c. Examination shows the presence of pneumothorax in the lower portion of the left chest. There is no activity on the right and only a few dry râles on the left side. There are no symptoms. Patient is working and feels well.

CASE 23.—*Patient*.—A. R., male, aged 42, laborer. Family history negative. Eleven years ago patient had a severe pulmonary hemorrhage. Returned to Italy, staying fourteen months. Nine years ago had another severe attack of hemoptysis. At the present time is coughing constantly, and during the past three weeks has raised blood at times in considerable quantity.

Examination.—May 12, 1911. Fairly well developed and nourished. Heart not remarkable. Consolidation with slight amount of activity is evident in the right upper lobe. On the left side there are signs of consolidation over the upper two thirds of the chest with cavity formation below the clavicle in front. Activity marked. Sputum positive.

Operation.—By means of thoracentesis in the midaxillary line on the left the patient was given 800 c.c. of nitrogen gas without discomfort.

Subsequent History.—We have so far been able to follow this patient for about two months. There has been a marked improveemnt in the general condition. Activity has entirely disappeared on the left side and signs of cavity formation are much less marked. There has been some gain in weight. No recurrence of hemoptysis. The outlook is very encouraging.

CASE 24.—*Patient*.—N. L., male, aged 19, student. Family and personal history negative. Fourteen months previous to April 29, 1911, patient developed a cough, accompanied by night sweats. Sanatorium treatment for three months, one year ago, gave only temporary benefit.

Examination.—Fairly well developed and nourished. Signs of consolidation are present above the level of the second rib on the right side and the fourth on the left, with only a slight amount of activity.

Operation—By means of thoracentesis 300 c c of nitrogen were injected in the anterior axillary line on the left side At this point, on account of severe pleural pain, the operation was discontinued Nitrogen had flowed slowly and with difficulty, as if under pressure In this case it seemed as if a small pleural sac probably surrounded by adhesions had been distended with the nitrogen

Further treatment was refused by the patient

CASE 25—*Patient*—J D, male, aged 17, student Family and personal history negative Beginning about three months previous to April 29, 1911, following a cold, patient developed pleurisy and has steadily lost in weight and strength

Examination—Fairly well developed and nourished Left chest was flat throughout to percussion with evidences of consolidation over the upper two-thirds At the right apex there was some evidence of infiltration

Operation—Thoracentesis was done in the eighth space in the left back, the needle apparently went through a mass of thickened pleura This case was therefore rejected as unsuitable for pneumothorax therapy

CASE 26—*Patient*—J A, female, aged 29, engaged in housework Family and personal history unimportant Patient presented herself for examination on May 5, 1911, giving a history of cough of ten days' duration, with pain in the chest, fever and some night sweats

Examination—Well developed and nourished Heart not remarkable Lungs show involvement over the upper lobe on the right with a slight amount of moisture and on the left side above the level of the third rib in front Sputum is positive

Operation—By means of thoracentesis in the left anterior axillary line 1,000 c c of nitrogen were injected, which was followed by a great deal of discomfort and weakness and a rapid rise of pulse These symptoms passed off in about twenty four hours

Subsequent History—This patient has been followed now for about two months There has been an improvement in the general condition and the right side shows no evidence of activity, There are very few evidences of moisture on the left Temperature has disappeared In this case the prognosis is good

CASE 27—*Patient*—G D A, male, aged 30, laborer Family history negative Pleurisy eight years ago For about one year previous to May 5, 1911, there has been more or less constant presence of cough with some expectoration and occasional night sweats At this date examination shows patient to be well developed Heart not remarkable Infiltration present in the upper left lobe Upper two lobes on the right are involved with considerable moisture Sputum is positive

Operation—One week following examination artificial pneumothorax was performed by means of thoracentesis in the anterior axillary line at the level of the fourth rib, and 400 c c of nitrogen were injected

Subsequent History—At the end of the period of observation the patient was taking 1,200 c c of nitrogen at a single injection Evidences of activity in the right lung following compression had entirely disappeared Patient is doing well

CASE 28—*Patient*—V T, female, aged 29, engaged in housework Family and personal history negative For about three months previous to May 6, 1911, patient has complained of considerable pain in the chest, cough, night sweats, with large amount of expectoration

Examination—Well developed and nourished Heart not remarkable Consolidation involving the upper lobe on the right side, with a moderate amount of activity, and on the left above the level of the fourth rib in front there is a marked amount of activity

Operation—By means of thoracentesis in the left axillary line 500 c c of nitrogen were injected without discomfort

Subsequent History.—Up to the present time, following several injections of nitrogen, expectoration has entirely ceased. Examination shows little or no activity in the chest, there being only an occasional dry râle. The outlook as a result of continued treatment is favorable.

In considering these cases, it should be noted that almost without exception they have been very unfavorable at the outset. In those where improvement has been shown during the first two or three months of treatment and in which it has been persisted in, there has been a continuation of benefit derived both as regards the physical and pulmonary condition.

DISCUSSION OF CASES AND CONCLUSIONS

The foregoing twenty-eight cases of phthisis have been subjected by us to artificial pneumothorax therapy within the past two and one-half years. With three exceptions all of the cases have been advanced ones which had previously failed to respond to methods of therapeutic hygiene.

The last eight cases have been treated by nitrogen injection too recently to draw conclusions as to the ultimate result of the treatment. It may be said however, that with the exception of the three cases in which a pleural space could not be established, a distinct relief of symptoms has been the immediate result of the lung compression in practically all of the reported cases of our series.

The tuberculous process has been brought to a standstill in at least six of the cases which have been under constant observation and continued treatment. In two instances there has been cessation of all activity in both lungs.

The promptness and willingness with which most of the patients responded to summons for repeated injections were conclusive evidence at least of the symptomatic relief attending the therapy. This might have been credited in part to psychic influences had there not been a corresponding improvement in the objective signs revealed by repeated examinations.

From experience with the earlier cases we have been led to the employment of more frequent injections. It cannot be denied that this factor is of paramount importance. The completeness of the compression is thus more nearly attained, furthermore, the partial mobilization of the lung permitted by the absorption of the nitrogen is promptly prevented by its early renewal.

The fatalities recorded were due to the unarrested progress of the disease in certain of the more advanced cases. In no instance was death referable in any way to the pneumothorax therapy.

"Pleural eclampsia" (Forlanini), or a reflex inhibition of the heart through vagus irritation from the pleura, is a danger to be considered in this treatment as in other therapy requiring thoracentesis. We believe

that it may always be prevented by anesthetizing the pleura as described in a previous paragraph

Air-embolism may result from the direct introduction of gas into a pulmonary vein This should never occur if the technic described above is faithfully observed

We have experienced no accidents, and believing that they are always avoidable, we conclude that pneumothorax therapy is a safe procedure

Pulmonary tuberculosis when essentially unilateral, and resistant to hygienic treatment, is in a certain number of cases arrested by the continuous employment of artificial pneumothorax therapy Our treatment has been of insufficient duration to permit us to claim a permanent cure in any one case We believe that such is possible, however, as proved by the recent reports of Brauer and Spengler

We conclude therefore, that artificial pneumothorax is entitled to definite recognition in the treatment of pulmonary tuberculosis

We wish to express our gratitude to Mrs C H Colburn, Mr Charles D Sias, and Dr Richard C Cabot for their contributions to the Massachusetts General Hospital sufficient to finance the erection and maintenance of a tent ward on the hospital grounds, where our cases were treated under special nurse supervision

We also express our appreciation of the courtesy shown one of us in Marburg, Germany, by Professor Ludolph Brauer, who demonstrated the results of treatment both in private and hospital cases, and contributed valuable instruction in the technic of his incision method

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CHRONIC FOCAL INFECTIONS AND THEIR ETIOLOGIC RELATIONS TO ARTHRITIS AND NEPHRITIS *

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There is nothing new in the principle involved in the subject of the paper It has long been known that acute rheumatic joint-infections are the result frequently of a primary infection of the faucial tonsils, or tissues about them Pneumonia is doubtless the frequent result of the sudden change of a non-virulent to virulent type of pneumococcus whose common habitat is the upper respiratory passages in city-dwellers It has been shown that a common source of infection in epidemic cerebro-spinal meningitis is the nasal mucous surfaces Acute endocarditis also has its source, in many instances, from the faucial tonsils Acute parenchymatous nephritis is frequently the result of the toxemia of diphtheria Acute gonorrheal arthritis has its source in a focal infection of the urinary or genital tract A local tubercuIous focus may cause systemic infection

SITE OF FOCAL INFECTION

1 The faucial tonsils, the peritonsillar tissues and supratonsillar fossæ In this may also be included the lymphoid tissue embraced in the pharyngeal tonsil and elsewhere in the nasopharyngeal space The lymphoid tissue comprised in the tonsillar tissues is most abundant in childhood, and frequently becomes atrophic in adult life The site of this tissue subjects it to infection of various kinds The abundance of this tissue in the child probably explains the frequency of infections like acute rheumatic fever, diphtheria, tonsillitis, etc, in the earlier periods of life The fact that chronic septic focal infection may lie latent in the tonsillar tissue has not been generally recognized That this focal infection may produce a chronic systemic disease is established by clinical experimentation

2 Abscesses of the gums and alveolar sockets, pyorrhea alveolaris and septic types of gingivitis may also cause systemic disease of various types

3 The various sinuses about the head — maxillary, ethmoidal, sphenoidal and frontal — may also harbor focal infection and cause systemic disease

4 Bronchiectatic and pulmonic cavities due to chronic disease may also produce chronic systemic infections

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5 Chronic ulcers of the gastro-intestinal tract, especially of the bowels This source is probably rare and more problematic than that of any other systemic infection

6 Chronic appendicitis Chronic catarrhal appendicitis may produce not only the local discomforts including disturbance of the functions of the digestive organs, but it may also be a focal source of systemic infection with the damage done chiefly to the cardiovascular apparatus

7 Cholecystitis and cholangeitis, with or without calculi, have been recognized as a source of systemic infection, the brunt of the damage apparently falling on the cardiovascular apparatus and kidney

8 The urinary tract, including the pelvis of the kidney, the bladder and more particularly the prostate gland Pyelitis of whatever type, even when there is only moderate obstruction of the drainage of the kidney pelvis, may produce myositis, arthritis, neuritis, etc

9 Genital tract The prostate and seminal vesicles are a common source of infection of gonorrheal arthritis and probably of ordinary septic infections The fallopian tubes and the uterus are less common as a source of chronic systemic disease in all probability It is said that the parametrium is a more common focal source of infection

10 Local, septic, submucous and subcutaneous foci anywhere in the body may be a source of systemic disease

THE SYSTEMIC RESULTS OF FOCAL INFECTION

1 Chronic arthritis is one of the most common results
2 Nephritis both acute and chronic
3 Cardiovascular degenerations
4 Chronic neuritis and myalgia (myositis)

The studies and experiments embodied in this paper are limited to the arthritides and to subacute and parenchymatous nephritis Of these, chronic deforming arthritis, commonly known as arthritis deformans, a chronic osteoarthritis of hypertrophic or atrophic type, is the form seen in the majority of the studies Next to the arthritides the largest number of cases comprise subacute parenchymatous nephritis and chronic parenchymatous nephritis

The work has been done on private and clinical patients in the Presbyterian Hospital The bacteriological and histological studies and the animal experiments have been carried on by Dr D J Davis and by Dr Homer K Nicoll

MODE OF PROCEDURE

The patient presenting evidences of chronic cardiovascular disease, nephritis or arthritis, is carefully examined in reference to previous disease which might be related to the existing condition and also for the existence of focal infections somewhere in the body When a focal point

of infection has been located and seems rationally related to the systemic infection, it is removed if possible, surgically or by some other means An attempt is made thoroughly to eradicate the focus of infection Appendectomy, drainage of the gall-bladder or of the pelvis of the kidney is insisted on not only because of local discomforts related to these diseases, but, what is quite as important, to prevent further systemic degeneration The prostate and seminal vesicles may easily be reached by the finger and the septic contents removed If necessary, vasectomy and drainage may be carried out Transillumination of the head may be made to determine the presence of sinusitis The skilled specialist is necessary to remove these conditions by operation or treatment The faucial tonsils should be enucleated Ordinary tonsillectomy leaves an abundance of lymphoid tissue which may be sealed over by the operative scar and leaves a worse condition than that for which the operation was made Adhesions between the tonsils and pillars of the fauces frequently wall in foci of infection in peritonsillar tissues The supratonsillar fossa may contain lymphoid tissue and continue a source of focal infection even when the faucial tonsil is removed Ulcerative gingivitis, small abscesses under the gums and collections of pus in the alveoli require vigorous treatment Ill-fitted crowns on teeth and much bridge-work may harbor septic infection in the mouth and produce systemic disease and when found should be removed

Careful examination of the tissues or secretions removed by manipulation or operations have been made microscopically, cultures of bacteria attempted and, in the work we have done, animal experimentation has been carried out in many instances

Illustrative conditions as found in patients suffering from chronic arthritis of a deforming type and subacute and chronic parenchymatous nephritis are included in this report So far, more than thirty cases have been under close observation whose original focal infection appeared to be in the tonsillar tissues It is impossible to give all of the results in these patients at this time because a good many of the patients are still under observation The result of the method of treatment in the majority of the patients has been most successful In two patients of the advanced type of chronic deforming arthritis, no beneficial result was obtained Following the report of the patients treated, the method of treatment will be further amplified

CASE REPORTS

ARTHRITIS

CASE 1.—*Patient.*—Mrs. A. P. R., aged 38, multipara had an osteo arthritis of left hip, which had existed for six years with shortening of the extremity and pain stiffness and lameness on exertion with gradually increased severity She had had four pregnancies with complicated deliveries, one miscarriage Patient was well nourished and presented, in addition to the disease of the left hip, hypertrophied and infected faucial tonsils ruptured perineum with a retro displaced

large uterus Blood hemoglobin 80 per cent, reds 4,350,000, whites 8,000 Twenty-four-hour collection of urine, 1,525 c c, specific gravity 1 010, acid, no albumin, no sugar, no casts, no red cells, few leukocytes *X*-ray of hip showed erosion of upper border of acetabulum with mushroom enlargement at junctuie of head and neck of the femur, some flattening of the head

Treatment and Animal Experiment—Plastic pelvic operation and uterine curettage was done by Prof J C Webster The tonsils were thoroughly enucleated by Dr George E Shambaugh From the cut surface of the tonsils a nearly pure streptococcus was obtained in culture A rabbit was inoculated with resulting acute multiple arthritis In a few days the animal died, and from the infected joints and the heart's blood of the animal pure cultures of the streptococcus were obtained

Course—The patient was given a modified rest cure Six months after leaving the hospital a letter from the patient stated that she was feeling well, could walk, play golf, ride horseback and perform any physical effort without discomfort A slight limp due to shortening of the left extremity remained

CASE 2—*Patient*—Mrs J W J, aged 40, quartipara, presenting a case of osteo-arthritis atrophica chronica, was first seen in January, 1907 For about eighteen months the patient had had swelling and stiffness and pain on motion with some deformity of the small joints of hands, feet, knees, wrists and elbows and more recently stiffness and lameness on moving, in the cervical and dorsal spine Previous condition of health was good During the whole period of illness she had had treatment for chronic arthritis in which salicylate of soda and other antirheumatic remedies were used Recently a "streptolytic" serum was given by deep injection, as much as 100 c c per day for four days and then repeated on the sixth Reaction with temperature of 102 F and general malaise followed each injection The patient was weak, nervous, with poor appetite and general stiffness on exertion in the affected joints Menstruation was regular

Examination—Blood, hemoglobin 50 to 55 per cent, reds 4,100,000, whites 12,500 Urine twenty-four-hour collection normal Tonsils moderately enlarged, adherent to the pillars of the fauces and crypts moderately infected General examination as to the organs of the body was negative Pelvic organs normal Many of the joints of the fingers were spindle shaped, crepitated on motion, both wrists were enlarged and fluctuated Swelling and tenderness of small joints of feet and more especially of the metatarsophalangeal, cervical spine, tenderness on motion Rest cure treatment and summer spent at Asheville, N C, gave no relief There was progressive development of the disease in all of the joints

Treatment—Aug 15, 1907, the tonsils were thoroughly enucleated by Dr Otto T Freer A rest treatment was then instituted with restorative tonics Treatment with syrup of iodid of iron immediately

Course—Following the tonsillectomy all of the joints became considerably worse and there was redness, swelling and pain on motion The patient could walk only with great discomfort In April, 1908, there was a great improvement The patient was able to walk 2½ miles a day without fatigue or pain There was still some deformity of the joints of fingers and some tenderness along the course of the right musculospiral nerve Blood examination showed normal condition In 1910 patient was reexamined and normal conditions found The patient expressed herself as feeling entirely well No cultures were made from this patient's tonsillar tissues

CASE 3—*Patient*—Mrs E W, aged 50, primipara with a osteo arthritis chronica of mixed type was admitted to the Presbyterian Hospital Oct 16, 1909 For two years there had been swelling, tenderness pain on motion and deformity of many of the joints of extremities It began in feet and hands and extended to larger joints and finally involved cervical spine The condition was progressive There was malnutrition loss of weight from 160 to 129 pounds For years the

patient had been subject to attacks of acute tonsillitis She had also suffered for years from pyorrhea alveolaris

Examination—Patient was poorly nourished, very nervous and irritable Her mouth was badly infected, with many stumps of carious teeth, some of them loose in the sockets, gums retracted and infected, tonsils large, rough, adherent to pillars of fauces and crypts infected Her breath was offensive Heart, lungs, abdominal organs and pelvic organs were normal There was swelling with some deformity of both ankles, right metatarsophalangeal, both knees, right middle and left fingers, the wrists and elbows Some contraction of hamstring muscles prevented complete extension of legs Both biceps tendons of arms contracted which prevented extension of forearm Twenty-four hour collection of urine was normal in amount and specific gravity and contained a few hyaline casts Blood hemoglobin 90 per cent, reds 4,600,000, whites 13,400 Oct 18, 1909, both faucial tonsils were enucleated by Dr George E Shambaugh and one week later the roots of carious teeth were thoroughly removed by Dr Frederick Moorhead From the cut surface of the tonsillar tissue a pure culture of streptococcus was obtained

Animal Experiment—A rabbit inoculated with a culture suffered from acute multiple arthritis and died in a few days The streptococcus was regained from the infected joints and from the heart's blood

Course—The patient was permitted to return to her home too soon and did not fully carry out directions as to rest treatment Some time elapsed before the alveolar processes were absorbed and the mouth remained sore April 3, 1910, she returned to the hospital where rest treatment was instituted with resulting marked improvement The patient gained in weight from 129 to 140 pounds After the return home frequent communications by letter with the patient and her physician have shown that the progress of the disease has entirely stopped Some of the deformities were so great that one could not expect entire anatomical restoration The last communication is dated December, 1911, in which the patient says that the strength of her upper extremities and spine is entirely normal There is some fatigue in the lower extremities after attempting to walk for any great distance, but there is a continued improvement even in this respect

CASE 4—*Patient*—J H male, married, aged 37, bookkeeper, with osteo arthritis hypertrophica chronica, was admitted to the Presbyterian Hospital Dec 9, 1909 There had been swelling, tenderness and soreness in the knees, ankles, left wrist and right jaw and right temporomaxillary joints, during the past four years The first trouble began in the right knee following a fall A diagnosis of tuberculous arthritis was made at that time and the knee-joint was injected with iodoform emulsion on four different occasions This gave no relief After one year the left knee became involved and this was also aspirated Then followed the involvement of other joints named Recently the patient has had tonsillitis, but does not recall that he suffered from the disease since childhood He denies venereal disease, has four healthy children, and is well except for the arthritis

Examination—Both tonsils were greatly enlarged, rough and many follicles showed cheesy masses Patient is unable to fully open the mouth Both knees greatly enlarged, the right measuring 40, the left 39 cm Motion limited Small rice like bodies can be felt in both joints Both ankles are swollen, tender, slightly limited in motion Spinal column is not involved General examination did not show any abnormal find of importance Blood hemoglobin 72 per cent (Dare), reds 4,750,000 whites 9,500 Prostate not enlarged, no exudate obtained from stripping prostate December 1909, both tonsils were thoroughly enucleated by Dr F Guerney Stubbs Cultures from cut surfaces of tonsils yielded hemolytic streptococcus in pure culture A rabbit inoculated with the streptococcus developed acute multiple arthritis and died in one week A streptococcus was obtained in pure culture from the joint exudate The heart's blood was sterile Fluid from the right knee to the amount of two ounces was cloudy, yellow and

sterile Patient left the hospital December 18, improved both as to joint condition and general health A report recently from him stated that he had practically returned to normal condition

CASE 5.—*Patient*.—Dr A W A, aged 40, married, with osteo-arthritis hypertrophica chronica of spine, was admitted to the Presbyterian Hospital March 20, 1911 Complained of stiffness and soreness with pain on motion in hips and shoulders which began five years before as an attack of apparent lumbago The condition gradually involved the whole back and during the previous winter pain had extended to the left side of the neck and radiated around the chest, making it difficult to breathe Stiffness and soreness increased after lying or sitting, aggravated by jars in walking or driving Periods of improvement followed by worse conditions At one time the joints of the fingers were involved during acute exacerbation of the spinal trouble He did not remember that he ever suffered from severe tonsillitis Had lost 30 pounds in the previous year Had a gonorrhea of mild type fifteen years ago

Examination.—Tonsils were small, adherent to pillars of fauces, and some of the crypts could be seen infected Heart and lungs were normal Abdomen was negative excepting for rigidity of abdominal wall Spinal column was rigid There was tenderness to pressure along the spinous process, some tenderness on motion of both shoulders and hip-joints but no crepitation Prostate was not enlarged, not tender and no exudate was obtained by stripping the glands March 25, 1911, both tonsils were thoroughly enucleated by Dr Geo E Shambaugh Tonsillar tissue small in amount, but small abscesses were found deep in the tissues from which a pure culture of streptococcus was obtained

Animal Experiment.—A rabbit inoculated intravenously developed acute arthritis which progressed into a chronic form of osteo-arthritis The animal lived nearly two months, became emaciated and at the time of death had several enlarged joints with exostosis and subluxation of the left shoulder A streptococcus was isolated from the exudate in the joints

Course.—The patient steadily improved, played golf during the summer and followed his professional duties A letter dated Dec 18, 1911, states "My general condition is extremely good I have added 30 pounds to my weight and have lost the sense of fatigue from which I suffered I can move much more rapidly and comfortably and rest well at night I still suffer from periods of decline, but these are very short in duration My spine has improved wonderfully, I can stand almost straight and the pain is almost gone There is still some limitation in motion especially in the neck, but there is steady improvement"

CASE 6.—*Patient*.—Dr E S E, aged 26, single, with polyarthritis subacuta was admitted to the Presbyterian Hospital March 2, 1911 Pain in both knees, left ankle, small joints of both feet, especially of the metatarsophalangeal and some soreness in lumbar spine Tonsillitis began ten years ago and, after that time an exacerbation of an arthritis of feet and knees was exaggerated Was obliged to go to bed Had an attack of tonsillitis with arthritis six years ago

Examination.—There was swelling and tenderness of joints named The tonsils were large, rough, crypts infected with whitish exudate Lungs and heart were normal, abdominal organs normal

After two weeks of treatment the patient was discharged as subjectively well Later the patient developed chronic arthritis involving small joints of feet ankles, knees and wrists In January, 1911, he had acute appendicitis which was operated on Before the patient left the hospital his tonsils were enucleated by Dr Friedburg

Animal Experiment.—A pure streptococcus was obtained in culture and inoculated into a rabbit Acute multiple arthritis developed and the rabbit continued ill for a considerable period and then recovered

Course.—Following the enucleation of the tonsils the patient passed two weeks in the country at rest Improvement was steady and progressive and by the

middle of September, 1911, he was entirely free from all joint involvements and able to return to his professional work

CASE 7.—*Patient*.—Mrs. C. C. M., aged 30, primipara, with osteo arthritis atrophica chronica, was admitted to the Presbyterian Hospital May 17, 1911. Patient complained of soreness, stiffness and swelling and some redness in the small joints of feet and hands, knees, shoulders and wrists. The joint-trouble appeared first in September, 1910, and continued until February, 1911, when there was a rather sharp exacerbation. The patient was always worse in the morning, had had no fever. She was nervous, had a good deal of occipital headache and pain in the back. Appetite and digestion were good, bowels moderately constipated. Average weight was 108 pounds. There was no disturbance of the urinary organs. Menstruation regular, lasting four days, but painful. Had a miscarriage three and a half years ago. Had frequent sore throat since an attack of scarlet fever when she was a child. Pain in left side few years ago, which was called "pleurisy."

Examination.—Patient was frail and sallow, tonsils enlarged, rough, adherent to pillars and yellowish exudate could be seen in crypts. Lungs and heart were normal. Abdominal organs appeared normal. Pelvic examination showed no abnormal condition. Urine, twenty-four hour collection, was normal. Blood hemoglobin 75 per cent., reds 4,600,000, whites 6,000. March 23, 1911, tonsils were thoroughly enucleated by Dr. George E. Shambaugh.

Animal Experiment.—A pure streptococcus was obtained in culture from the cut surfaces. This inoculated into a rabbit produced an acute multiple arthritis. The animal died and the culture of streptococcus was obtained from the exudate of the joints.

Course.—Twenty-four hours after the enucleation of the tonsils, patient left the hospital without my knowledge. She kept up and about and suffered more with joint-pain than for a long time. She was then put to bed on a rest cure treatment and immediate improvement occurred. Sept. 25, 1911, patient reported herself as improved in every way. Joint-trouble was practically gone. She still complains of lessened strength and endurance.

CASE 8.—*Patient*.—Miss M. I. P., aged 39, nurse, with arthritis atrophica chronica, was seen first Dec. 7, 1910. Patient complained of swelling and stiffness in both knees which began a year and a half ago, constantly present, but periodically worse. There was no pain when patient was quiet, it was aggravated by motion and fatigue. Left index-finger became involved in 1910 and later the right elbow. Tonsillitis off and on for four years. Had noticed an increase of joint disturbance with tonsillitis. General condition was good. Bowels regular, menstruation normal.

Examination.—Patient well nourished. Teeth good, mouth clean, tonsils enlarged, rough, both infected, right more than left. Heart and lungs normal, abdominal organs negative. Blood hemoglobin 85 per cent., reds 4,600,000, whites 9,000. Urine, twenty-four hour collection, showed normal condition. Both knee-joints were swollen, crepitated on motion and were tender. No exudate. Right elbow swollen and tender. Left index-finger spindle-form. Tonsils enucleated by Dr. George E. Shambaugh.

Animal Experiment.—Cultures made from cut surfaces of tonsils gave a streptococcus in almost pure culture. Streptococcus injected into rabbit produced acute multiple arthritis. The animal died and from the exudate of the joints and the heart's blood a pure culture of the streptococcus was obtained.

Course.—June 27, 1910, patient wrote that she had taken a rest-cure for ten days and had resumed her work in a graduated way. There had been slight but gradual improvement until about middle of May, then she rapidly improved and considered herself entirely well.

CASE 9.—*Patient*.—Mr. I. M., aged 27, single, traveling salesman, with osteo arthritis hypertrophica chronica, was admitted to the Presbyterian Hospital May 25, 1911. He complained of limitation of motion and pain in right elbow, both

knees, left sternoclavicular and left temporomaxillary Trouble began three years ago, onset insidious It began in knees with swelling, pain on motion Two months later toes, fingers, elbows, shoulders and jaw became involved Patient was treated at hospital in Pittsfield, Mass, and cast put on one knee This gave temporary relief Since that time the course had been one of exacerbation and decline, but the patient had never been free from some debility He had had scarlet fever with double otitis media when a child He denied venereal disease, did not remember to have suffered from tonsillitis

Examination—Right forearm could not be fully extended because of contraction of biceps muscle Elbow-joint was not involved Left knee joint was swollen with effusion into synovial sac Soft structures about joint were boggy and thickened, hamstring muscles contracted Right knee-joint showed abnormally free motion There was exostosis on external surfaces of outer condyle Left sternoclavicular articulation was moderately swollen, tender and painful on motion and mouth could not be fully opened Other joints were normal Lungs and heart were normal Mouth was clean, teeth sound Tonsils were not enlarged, but were ragged and buried between adherent pillars, showing point of exudate in follicles Abdominal organs were normal Prostate was not enlarged and no exudate could be obtained upon stripping the organ The urine in single and twenty-four hour collection was normal Blood hemoglobin 76 per cent (Dare), reds 4,100,000, whites 8,400 The tonsils were thoroughly enucleated by Dr George E Shambaugh Thirty c c of a clear fluid was obtained from the left knee joint This was sterile and microscopically only a few polynuclear leukocytes were shown

Animal Experiment—A streptococcus in pure culture was obtained from the cut surfaces of the tonsils A rabbit inoculated developed acute multiple arthritis and died in a few days A pure culture of streptococcus was obtained from exudate of joints

Course—Autogenous vaccinations were made and used on this patient every week or ten days June 25, he showed marked improvement and in September he returned to his usual occupation which he followed without much discomfort December 22 the patient wrote that his condition was much improved and that there was practically no pain in the joints and very little if any stiffness Slight swelling still remains in the left knee He had had three vaccinations and to the vaccinations he ascribed much of his improvement

CASE 10—*Patient*—W J F, aged 38, married, brewer, with arthritis rheumatica chronica, was admitted to the Presbyterian Hospital Sept 11, 1911 He had suffered from attacks of rheumatism, beginning when he was 17 years old, with frequent attacks during the last twenty-one years Finally chronic arthritis resulted There was a decided rheumatic family history Patient had gonorrhea fifteen years ago from which he made a good recovery On admission to the Presbyterian Hospital he presented swollen, painful right ankle, right index and second fingers and right elbow Tonsils were enlarged, rough and infected The left border of the heart measures 12 cm from the midsternum A soft systolic murmur was heard in right second interspace not transmitted Urine examination normal, including specimen and twenty-four-hour collections Blood-examination, normal find Prostate not enlarged and exudate could be stripped from the gland September 26 the tonsils were thoroughly enucleated by Dr George E Shambaugh

Animal Experiment—From the cut surfaces of the tonsils almost pure cultures of the streptococcus were obtained This inoculated into a rabbit produced acute multiple arthritis from which the animal died in a few days The streptococcus was reobtained from the joint exudate and heart's blood

Course—Phenomenal improvement followed the enucleation of the tonsils The first two or three days the joints were more swollen and painful Then immediately began improvement and for the first time in many years the patient is now entirely free of arthritis

These case histories are good examples of arthritis deformans and include but a few of the many who have been so managed, but are sufficient in number to illustrate the principles of the paper

SUBACUTE AND CHRONIC PARENCHYMATOUS NEPHRITIS

CASE 1.—*Patient*.—Miss L. R., aged 22, of Chicago, was admitted to the Presbyterian Hospital Sept. 11, 1909. Three or four years previously she had had an attack of acute tonsillitis with bronchopneumonia. Following this, edema of face and hands developed, a pasty pallor, headache and nausea, and it was found that the urine contained albumin and a good many hyaline, granular and epithelial casts.

Examination.—Marked pallor, edema of face, lower extremities with some free fluid in the abdominal cavity. Heart and lungs negative. Liver not enlarged. Spleen not palpable. Blood 4,000,000 reds, 18,700 whites, 63 per cent. hemoglobin (Dare). Urine twenty four-hour collection 900 c.c., specific gravity 1.020, much albumin, many hyaline and granular casts, much blood. Arterial tension (Stanton), 145 mm. systolic. Tonsils very large, rough, infected, with adhesions to the pillars of the fauces.

Treatment.—The patient was kept under treatment at the Presbyterian Hospital from September 11 to November 13, on a suitable diet, free bowel actions every day and an iron alkaline treatment with gradual improvement in general condition with a better urine output, less general dropsy, with an improvement in the blood condition, but on the whole the patient did not advance much toward recovery. Therefore, Jan. 5, 1910, she was again placed in the Presbyterian Hospital and the tonsils were thoroughly enucleated by Dr. F. Guerney Stubbs. The patient made an uneventful recovery from the tonsillectomy. The patient was kept quiet on a suitable diet, restorative tonics, etc. January 19 the twenty-four hour collection of urine was 1,470 c.c., specific gravity 1.015, albumin 0.08 per cent. Three fine granular casts were found in the centrifuged specimen, no blood, no leukocytes. Before this date the albumin was larger in quantity. There were always many casts and a good many red cells and leukocytes. From this date on the urine slowly cleared up.

Course.—The general condition of the patient improved until the winter of 1910 and 1911. When in the south (San Antonio, Tex.) she acquired broncho pneumonia and was severely ill for a time. Nevertheless recovery from this condition followed with a continued improvement of the kidney and general condition. June 24, 1911, a morning specimen of urine showed no serum albumin, no casts, no blood, no leukocytes. An evening specimen, specific gravity 1.024, showed no albumin, no casts, no blood. The blood at this time showed hemoglobin 90 per cent., reds 5,400,000, whites 8,000. General hygiene was continued and at the present time the patient is practically well. October 17, 1911, there were 1,400 c.c. of urine, specific gravity 1.012, no albumin, and the sediment from a fresh specimen examined at the same time showed no leukocytes, no blood cells, no casts.

CASE 2.—*Patient*.—J. H., schoolboy, aged 13, was admitted to the Presbyterian Hospital from the Central Free Dispensary on Dec. 4, 1909, suffering from subacute parenchymatous nephritis of the hemorrhagic type. He was operated on for hernia at the Presbyterian Hospital in September, 1909, and left the hospital well. He suffered from tonsillitis three weeks previous to second admission for which no treatment was given. One week previously he vomited in the morning after breakfast, again at dinner and supper time. Frequent urination occurred at the same time and it was noticed that the urine was red in color. He became thirsty, with weakness, dizziness and two days ago he vomited up some bright red blood. Since then he had been in bed. He had scarlet fever two years ago, no other disease excepting hernia for which he was operated on, as mentioned. He had had severe attacks of acute tonsillitis.

Examination.—Poorly nourished boy, marked pallor, edema of eyes, face and some of the lower extremities. Heart and lungs negative. Abdomen negative

Blood-pressure in recumbent posture 135 to 145 mm systolic Tonsils large rough and infected Temperature slightly elevated but subfebrile Pulse and temperature practically normal Blood reds 3,250,000, whites 9,400, hemoglobin 50 per cent (Dare) Urine twenty-four-hour collection 1,200 c c, specific gravity 1 008, cloudy, red with blood, acid reaction Albumin 0 1 per cent by weight Many twenty-four-hour collections of urine were made with practically same results Tonsillectomy was advised and enucleation of tonsils was done by Dr F Guerney Stubbs January 17 The boy made an uneventful recovery from the operation He was kept quiet in bed on a suitable non-nitrogenous, non-salt diet, the bowels were free and as soon as the hemorrhage in the urine ceased, he was given restorative iron tonics The blood improved gradually January 10, a little more than a month after admission, the reds were 4,500,000, the hemoglobin about 70 per cent Urine, the same date, 1,500 c c, specific gravity, 1 010, acid, albumin present in small quantity, no blood, no casts, a few leukocytes Subsequent examination of the boy during the summer of 1910 showed restoration to the normal

CASE 3.—*Patient*.—Dr R N S, aged 26, of Chicago, was first seen on Dec 13, 1909, and was admitted to the Presbyterian Hospital on Dec 15, 1909 Patient came because albumin had been detected in the urine in October, 1909 As high as 2 per cent by measurement had been found A few hyaline and finely granular casts had also been detected Patient tired easily, had some dull headache and was worried much about kidney condition He had suffered from attacks of tonsillitis for years past, had one attack during last winter He had smoked to excess until recently

Examination.—Tonsils large, red, ragged, infected Otherwise throat and mouth normal Chest, heart and lungs negative Abdomen negative No edema of lower extremities Urine specimen showed specific gravity 1 024, a good deal of albumin, not measured, many hyaline and granular casts, no blood The arterial tension with the Stanton instrument was 95 mm systolic Blood hemoglobin 85 to 90 per cent, reds 4,500,000, whites 8,600

Treatment and Course.—Dec 16, 1909, the tonsils were thoroughly enucleated by Dr Rhodes Since that time the patient has been examined and the urine is found entirely clear, and the patient remained in good health A letter from the patient, dated Dec 20, 1911, states that the urine is free of albumin and casts "Am feeling well and have had no evidence of nephritis for the last year and a half"

CASE 4.—*Patient*.—R Y, aged 18, schoolboy, was first examined May 13, 1910 A year and a half preceding this time a physician had found albumin and many leukocytes in the urine There had been no headache, no edema and, the patient thinks, no fever He had suffered from scarlet fever, pneumonia twice the last time one year previous to examination and had had many attacks of tonsillitis

Examination.—Well-developed, well-nourished boy of fairly good color The lymph-nodes in posterior triangles of neck moderately enlarged Tonsils enormously enlarged, red, ragged, and crypts filled with yellowish exudate Heart and lungs both normal Abdomen negative No edema of face or legs A specimen of urine showed specific gravity of 1 012, albumin in rather large amount and the microscope showed hyaline and granular casts, and a few kidney epithelia and leukocytes The arterial tension 130 systolic

Treatment and Course.—The important relation of the kidney to the infection of the tonsils was explained to the parents and the attending physician, Dr W S Picotte of Ishpeming, Mich, and thorough enucleation of the tonsils advised This was done, but I fear inadequately, during the summer of 1910 The patient spent the next winter in Florida in school and reported that his general condition had been much improved On Sept 12 1911 he came for examination The bases of both tonsils still remained and were red somewhat infected, the general condition good the urine acid, a faint trace of serum albumin but no casts and no leukocytes Arterial tension 125 The condition was explained as improved

and regret expressed that the tonsils had not been really enucleated Patient was advised to have urine reexamined from time to time and if albuminuria continued to have remaining portions of tonsils dissected out

CASE 5.—*Patient*.—Miss S T, aged 20, was first examined through the courtesy of her physician, Dr Albert Smith of Parsons, Kansas, July 6, 1911 The complaint was extreme weakness, swelling of the lower extremities, the abdomen and anemia The history showed that in November, 1910, the patient had a cold with infection of the throat About a month later patient became very tired at a dance and it was noticed that the feet became swollen Albumin and casts with blood were found in the urine The patient was taken to Texas at some mineral springs and drank quantities of water Rapid edema of face, extremities and body resulted She had had no headache, no fever and no disturbance of vision, slight cough recently The patient had scarlet fever at 7 years of age

Examination.—A tall slim girl, very pale, marked edema of face, lower extremities, free fluid in peritoneal and a moderate amount in both pleural cavities Few lymph-nodes palpable in posterior triangles of neck Apex of heart 8 cm from midsternum A blowing murmur over the pulmonary area Arterial tension 140 mm systolic, pulse 78 per minute, temperature normal Blood hemoglobin 53 per cent (Dare) Urine specific gravity 1 012, much albumin, many hyaline and granular casts and many red cells and leukocytes A good many kidney epithelia The patient was placed in Presbyterian Hospital on an appropriate salt-free diet At the hospital the urine measured in twenty-four hours from 600 to 650 c c on different days, specific gravity 1 018 to 1 020, contained a great deal of albumin, many hyaline and granular casts, many leukocytes and kidney epithelia and a good deal of blood

Treatment and Course.—The tonsils were enucleated by Dr Friedburg and the weakness of the patient necessitated two operations with an interval of one week between The dropsical condition gradually diminished and the patient improved in general condition July 21 there were 1,620 c c of urine, specific gravity 1 010, with less albumin, fewer casts and no blood July 29 the total urine was 1,620 c c, specific gravity 1 010, little serum albumin, few hyaline and granular casts, few red cells and few leukocytes and kidney epithelia At this date the patient left the hospital and spent the remainder of the summer in Canada following out a rest treatment with non-nitrogenous salt free diet and a restorative tonic of the syrup of the iodid of iron, free bowel actions daily Sept 29, 1911, a reexamination showed a much improved condition There was but a trace of albumin in the urine, very few hyaline casts, the dropsy had entirely disappeared except that when the patient was up and about for the greater part of the day, there was a slight swelling about the ankles The red cells were 4,800,000, hemoglobin 65 to 70 per cent, whites 10,000 A letter recently from the patient's mother tells of still further improved condition Dec 23, 1911, the urine examined showed specific gravity 1 015, yellowish-brown color, small amount of serum albumin and centrifuged deposit showed few leukocytes and two hyalo granular casts Jan 4, 1912, a letter from her physician, Dr Albert Smith, states that the physical examination showed a slight edema above each ankle Patient looked well, had gained in weight and strength Blood count at that date showed 4,252,000 reds, 8,200 whites, 80 per cent hemoglobin, and a letter from the mother of same date states that the patient is feeling fine, does not seem to have any aches or pains and is gaining in flesh and strength

CASE 6.—*Patient*.—Mr C L P, aged 23, foreman in wholesale tailoring establishment, Chicago, was examined May 6, 1911 He came for examination because albumin and blood had been found in urine Patient was easily exhausted after exertion and also early in the morning He slept well as a rule Appetite was not disturbed Bowels moved regularly Patient had had varicose veins of legs for a long time, had suffered from acute tonsillitis on several occasions during the last few winters He had typhoid at 12 years of age, no other serious illness

Examination.—Moderate pallor of skin, no enlargement of lymph-nodes Tonsils both very large and infected Heart apex 9 cm from midsternum left

border 11 cm No irregularity First sound moderately rough and impure No accentuation of second sounds Lungs normal Abdominal organs negative No edema of lower extremities Urine showed a great deal of albumin, many casts, red cells, leukocytes and kidney epithelia Blood hemoglobin 70 per cent, reds 4,000,000, whites 8,000 Arterial tension 110 mm systolic Condition of kidneys and probable relation to local infection of tonsils explained to the patient, and he was advised to have the tonsils thoroughly enucleated

Treatment and Course—Nov 4, 1911, the patient was seen by request He had had the tonsils thoroughly enucleated by his own physician and had had a month's vacation which he spent in the country on simple non-nitrogenous food and had kept the bowels moving freely every day At this time a specimen of urine contained no albumin, no casts, no red cells and only a few white cells The patient expressed himself as feeling entirely well Nov 4, 1911, a specimen of urine examined, showed no serum albumin, no casts, a few leukocytes, no reds

Reports of other cases are not made at this time because it would make an article of this kind too long, but subsequent reports will be made on other patients

THE EFFECT OF THE INOCULATION OF ANIMALS WITH THE CULTURES OBTAINED FROM INFECTED TISSUES

It is noteworthy that the streptococcus obtained in almost pure culture from many of the patients, when inoculated into animals, produced an acute arthritis either single or multiple, and in many of the animals produced an arthritis of deforming type Furthermore, from the dead animals' tissues the streptococcus has been again obtained in cultures It is also true that the cultures from the tonsils of patients who had no evidence of systemic infection contained the streptococcus practically identical with those patients who had systemic disease Inoculation of the strains of the streptococci obtained from the tonsils of individuals, without systemic disease, has not yet been experimented with enough to know what the result on animals would be It is an experimental fact that the streptococcus of any source may produce acute joint-lesions in inoculated animals, especially rabbits In most of the animals inoculated with the strain of streptococcus obtained from our patients, the usual acute arthritis occurred In some of the animals the joint-process became chronic and developed the marked anatomical changes (exostoses, rice bodies atrophy of cartilage, subluxation etc) found in osteo-arthritis of man It is also notable that in three of the patients suffering from nephritis, the strain of the streptococcus obtained from the tonsillar tissues of these patients produced albuminuria in the inoculated animals No other strains produced albuminuria

A few of the patients have been treated with autogenous vaccines The vaccines invariably produced reactions when injected in the dose of from 10 to 500 millions This reaction consisted of marked tenderness redness and swelling and frequently of rise of temperature of varying degree with constitutional disturbance in the form of general discomfort, aching muscles, headache etc Leukocytosis of varying degree would sometimes follow the injections Tenderness in joints would also sometimes occur

with the vaccinations So far it cannot be said that the autogenous vaccinations have been of any especial value in a group of patients Individual patients have apparently shown greater improvement with the vaccinations than without them

General hygienic treatment has been necessary in all the classes of patients treated and one would naturally infer that this general treatment had a good deal to do with the result With the arthritis cases it has been found just as necessary to continue a long and yet variable rest treatment with good food, restorative tonics and the various forms of individual treatment usually employed in the management of this group of diseases Assistance has been rendered by Dr John Ridlon, Dr Charles A Parker, Dr E W Ryerson, and others in the arthritis cases, by such measures as were found necessary in individual patients Casts have been applied to extremities, or to the spine, contracted tendons have been stretched and other necessary manipulations and corrective measures used

In those patients who, for some reason could not or would not follow out the details of after-treatment, rest, etc, improvement was not as soon obtained or not as fully secured as in those patients under command This, however, does not mean in my opinion that the final results are due to the after-treatment alone, for in past years the same care in the general treatment did not give the same degree of good results that has been obtained in later years by the methods suggested in this paper

FURTHER EXPERIMENTATION NECESSARY

It naturally occurs to one that there must be some other element present in individuals or something lacking in some patients which permits the systemic disease to attack them while others escape who present practically the same local condition with chronic focal infection Many people suffer from chronic hypertrophic tonsillitis with chronic infection, or an excess of lymphoid tissue in the nasopharynx with consequent anatomical obstruction and lack of drainage, or have chronic sinusitis, or chronic focal disease in other portions of the body and yet appear to be entirely well Naturally the hypothesis suggests itself that there must be some protective agency present in certain people and lacking in others It is a well-known fact that traumatism, excessive fatigue, general debility from some previous exhausting disease or exposure may be the beginning of an arthritis We commonly speak of this as a less resisting power in the individual Can we by some means ascertain what the essential lacking element may be in the individual whose joints are attacked from an existing focal infection? The specificity of the bacteria obtained by cultures from focal infections could probably be proved by investigation of the reaction to blood-serum, the spinal fluid and the exudate in the joints or elsewhere of patients suffering with systemic disease and some light could probably be thrown on the question by the research into the question of bacterial reaction to the blood spinal fluid, urine, etc, of

patients who have focal infection without systemic disease A further study would be of value also of the opsonic index and other specific reaction of the blood, spinal fluid, joint fluid, etc of individuals before and after autogenous vaccinations or after inoculations of polyvalent horse-serum made by injection into the horse of several strains of streptococci obtained from patients Research of this kind is under way in the work which is now being done and it is to be hoped that a later report may explain some of the conditions which are now obscure

I think that there can be no doubt that the insidious slow, degenerative processes which occur in many patients who arrive at the meridian of life are due to slow intoxications from chronic focal infections variously located The medical literature is full of statements of auto-intoxications from the intestinal tract and it is not improbable that this may be a source It is a fact that with proper hygienic management in diet, exercise, free excretion through the bowels, kidney, skin, etc, retrograde changes are delayed and an individual's health much improved thereby, but it is also true that with these measures fully carried out many people still show progressive interstitial nephritis with cardiovascular changes in spite of the best hygienic management Not infrequently it has been my experience to find that such patients suffer from a chronic infection of the gall-bladder, appendix or prostate, or some other focal infection The result of the removal of these infections has also been most astounding in many instances This paper would be too long to discuss further that part of the result of focal infections I hope to present that phase of the subject in another paper in the near future

THE NECESSITY FOR THE REMOVAL OF FOCAL INFECTIVE PROCESSES

It is not the purpose of this paper to advocate unnecessary surgical procedure It is, however, necessary to do something radical when one finds a patient who suffers from a focal disease that may produce acute disease or chronic degenerative changes in any of the organs of the body Excessive amounts of lymphoid tissue of the faucial tonsils or naso-pharynx in children is a double menace With obstruction and want of drainage those localities produce not only alterations in the bony framework of face and chest but offer a source of systemic infection which may be ruinous to the individual There can be no other reason for the prevalence of rheumatic fever in children than the frequency of local infections in throat and nose Quite as frequently children have endocarditis without other symptoms or rheumatic infection which has its source in the throat There may possibly be a reason for the retention of some of the lymphoid tissue in the faucial tonsil but so far the physiologists have not been able to give a reason for its retention Nor I think, has there ever been an argument advanced to show harm from

the practical enucleation of all of this tissue I think anyone who has noted the difference in the physical and mental makeup of a child before and after the removal of large amounts of lymphoid tissue in the throat must be convinced that the change is due not only to a better air-space, but also probably to the removal of a constant, even though it may be slight, systemic infection It is an interesting observation of Dr Thomas L Gilmer and of others, of foci of specific infection about the gums and the presence of abscesses about the roots of the teeth, often unsuspected which must be recognized as a source of systemic infection that has not received the attention from the medical profession which it deserves I think that any one who has seen the illuminating results of a better physical health in patients whose dirty mouths have been made as nearly as possible clean, must be convinced of this source of systemic infection

I think that the specialist as well as the general practitioner has not fully recognized the importance, not only of the relation of the focal infection to systemic disease, and have not been fully awake to the necessity for entire eradication of the focus Partial removal of the faucial tonsils by whatever means frequently leaves a condition as bad as the original one, or worse An infected tonsil or tonsillar tissue need not be large in bulk In some of our patients small and apparently innocent tonsils contained abscesses from which pure cultures of streptococci were obtained The scar of operation may seal over infected crypts in lymphoid tissue An incomplete operation on the mouth may still leave alveolar abscesses In several instances of patients included in this series, more than one operation on the tonsils have been made necessary because of incomplete removal of the focus of infection by the first operator

The purpose of this paper has been to call the attention of the profession to a source of general disease which, while recognized by a few, is entirely ignored by the many No one would have the effrontery to say that the lack of recognition of the focus of infection is absolutely detrimental to the best interest of the patient, nor would one say that the treatment advocated is specific in that all patients are made whole and well by it, but it is believed that there is a principle involved as a cause of systemic disease which should be recognized, should be sought for more frequently and when the focal infection, wheresoever it may be located, seems to be related to the systemic disease, radical measures should be instituted to remove it When this is done, those general measures which long have been recognized as essential to the well-being of an individual should be instituted so that nothing will be left undone which may restore an invalid to health So far the experimental work done seems to prove clinically the truth of the principle advocated

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CHRONIC ORAL INFECTIONS*

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In 1891 Miller, in the preface to a series of articles[1] entitled "The Human Mouth as a Focus of Infection," says

> During the last few years the conviction has grown continually stronger among physicians, as well as dentists, that the human mouth as a gathering-place and incubator of pathogenic germs performs a significant rôle in the production of varied disorders of the body, and that if many diseases whose origin is enveloped in mystery could be traced to their source, they would be found to have originated in the oral cavity

Miller isolated fifty-eight varieties of microorganisms from the mouth, many of which are pathogenic or may under favorable circumstances become so.[2] These findings were verified by Black, Vincentini and others.[3]

When it is realized that in some or all mouths there may be found at times bacteria of most infections, the importance of the study of the mouth as a focal cause of disease becomes apparent. For instance, tubercle bacilli are found in the mouths of non-tuberculous patients. When the cervical glands are found to be tuberculous there can be little doubt but that the bacilli often reach the glands from the mouth through alveolar abscess, the tonsils, or through any suppurating focus in the mouth.

The prevalence of tubercle bacilli in the mouths of those not tuberculous is indicated by the experiments of Gilberti.[4] He injected guinea-pigs, previously subjected to the tuberculin test, with mixtures of inguinal and also of cervical glands taken from children dead of non-tuberculous disease, so far as known. Of thirty animals injected with the cervical-gland mixture, eleven died from tuberculosis. Of those injected with the inguinal-gland mixture, only two died of tuberculosis.

As a result of food wedging in between teeth malposed, or between approximating teeth having cavities of decay, or between teeth with improper restored contours, the gum septum is destroyed and deep pockets are formed. The injudicious use of crowns and bridges made as substitutes for lost teeth, and their faulty adjustment are sources of great danger, since they form pockets which harbor bacteria and are irritants to the gums, peridental membrane and alveolar process. These pockets

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1 Miller: Dental Cosmos, September, 1891, p. 689.

2 MacFarland: Pathogenic Bacteria, Ed. 4.

3 Bacteria of the Sputa and Cryptogenic Flora of the Mouth, London, 1897.

4 Gilberti: Medical Practice Series, 1910, iii, 313.

constantly present granulating walls and afford good incubating centers for pathogenic and other microorganisms, both aerobic and anaerobic Unfilled cavities of decay in teeth always harbor both saprophytic and pathogenic microorganisms, also unsterilized pulpless root canals or root canals containing gangrenous pulps or their septic remains, may be equally prolific as incubating centers

Many persons are mouth-breathers, either occasionally or generally, owing to stenosis from malformation or disease of the nasal fossæ The nasal fossæ offer barriers to the passage of bacteria through their labyrinthine formation, the hairs and the agglutinating material found on their walls The mouth offers practically no such obstructions Those having nasal stenosis breathe largely through the mouth, as a result there are admitted to the oral cavity, pharynx and tonsils, greater numbers of bacteria than when the nose performs its function normally There may be other causes for lesions of the tonsils, but it is highly probable that the constant passing of bacteria over them from a diseased mouth is the most potent That bacteria may pass through healthy tonsils, without causing them to become diseased, has been demonstrated by Wood [5] Some however, find convenient lodging places in the crypts of the tonsils, where they may remain until from some cause they become active and produce local or general infection

CHRONIC ALVEOLAR ABSCESS

Chronic alveolar abscess is so common that few go through life without one or more such suppurations There are two forms of this disease, that which continually or periodically discharges either into the mouth, nose, maxillary sinus, or elsewhere, and the blind abscess which never discharges through a sinus the pus being absorbed by the granulating walls of the abscess The former, discharging pus and bacteria as indicated, cannot but be prejudicial to health, and the latter, the blind abscess, offers greater danger Its presence is generally unobserved by the patient and may be overlooked by the physician, even if the mouth is examined, since it may not present to the eye any clinical evidence of its presence I think 25 per cent a safe estimate of the percentage of jaws having suppurating cavities That greater havoc is not wrought by such foci of infection is due either to the fact that the dosage of bacteria and their poisons is usually insufficient, or to the fact that the normal individual becomes immune Instances, however, are not lacking which demonstrate that such foci of infection are instrumental in causing neuritis, neuroses and secondary infections of the eye, ear and other parts, therefore when there are manifestations of disease which may be dependent on some local focus of infection, the mouth and jaws, as well

5 Cited by Sewall Jour Am Med Assn, Sept 9, 1911, p 869

as other possible sources should be examined to discover if they may not hold the key to the solution of the problem

Cervical and submaxillary adenitis is especially common in children having diseased teeth and jaws Frequently the glands are removed and their unsuspected cause, alveolar abscess, left untouched Odenthal[6] found glandular swellings in 99 per cent of all children who suffered from badly decayed teeth (abscessed teeth), and only 49 per cent in those having sound teeth

The question which has not been answered, but must and will be, is What is the bacteriology of chronic alveolar abscess? When this question and the question of susceptibility and immunity are answered, we can better understand the relation which these pathological cavities in the maxillæ bear to lesions in the heart, kidneys, lungs, joints, nerves and brain Here are possibilities not to be ignored Did similar abscesses exist in other bones of the body, their presence would demand attention, both by the patient and by the physician Alveolar abscess is usually considered inconsequential and when the attention of the profession has been called to it, it has generally excited little interest and has been allowed to pass as an insignificant "gum boil"

Acute alveolar abscess usually manifests itself in pain, swelling, rigors and fever, but the chronic form often gives no evidence of its presence Following the subsidence of the acute attack, the patient will often be unaware of the continuance of the condition, but unless the tooth causing it is removed, or has its pulp canal or canals disinfected and filled, the chronic form ensues and continues indefinitely, as it is rare that spontaneous cure takes place Owing to the tortuous shapes of some root canals it is not possible in all cases to sterilize completely and fill them to their ends, and even if the roots are rendered sterile through canal disinfection the chronic condition is not always cured A part of the apical portion of the root in such abscesses is often denuded of its peridental membrane by suppuration Between this portion of the root divested of the soft tissue attachment and the adjacent granulation tissue a pocket forms which is a breeding place for microorganisms that induce continuous reinfection

The salivary glands are doubtless occasionally infected by bacteria from the mouth I have seen two cases of infection of the parotid gland which seemed to be traceable to an infected mouth, and several cases of infection of the submaxillary gland which could be traced to no other source

It is but natural and proper that patients suffering from endocarditis, renal, joint and other lesions, outside the mouth, should consult the internist, orthopedist, or neurologist On this account the oral specialist has little opportunity to tabulate cases which throw any light on the

6 Odenthal Thérapie des maladies infectieuses, p 256

constitutional relation existing between the disorders before-mentioned and chronic infections in the mouth I have frequently found marked improvement in the health of patients following the cure of diseased conditions in the mouth, but the treatment has not usually been instituted with other idea than the removal of a local lesion The following case reports will illustrate this

CASE 1.—Some years ago, a man, a little beyond middle life, consulted me relative to a trivial dental lesion On making a careful examination of the entire oral cavity, I found several small sinuses discharging pus above the bicuspid teeth on one side of the upper jaw When these openings were explored with a sharp steel probe, a large cavity was discovered in the bone, the result of alveolar abscess, the presence of which was unsuspected by the patient On inquiring into his physical condition, I learned that for the past year he had had a cough, his digestion was impaired, and much of the time his temperature was slightly above normal He had frequently consulted his family physician, who examined his heart, lungs, sputum, urine and blood These gave no clue to the cause of his ill health His appearance indicated a toxemia I removed several teeth, curetted the abscess in the jaw and gave suitable after-treatment The fever at once subsided, the digestion was soon much improved and the cough was lessened and finally disappeared altogether Although seemingly the patient's physician had made a careful examination, he had overlooked one important factor, the mouth

CASE 2.—Mrs C., aged 30, noticed the appearance and disappearance at frequent intervals of an erythemic patch about the size of a silver quarter on the skin over the canine fossa On examining the mouth for a possible cause for this reddened condition of the skin, I found the lateral incisor pulpless There was no sinus, the tooth had given no trouble The only evidence of disease found in the mouth was a slight hyperemia of the gum over the lateral incisor root indicated The radiograph showed a pus cavity in the bone at the end of the root about the size of a large pea Disinfection of the root did not effect a cure I made an opening through the labial wall of the alveolar abscess, excised the end of the root and curetted the cavity The erythemic patch on the cheek disappeared and did not return

CASE 3.—Mr S., aged about 25, was directed to my clinic for the treatment of a chronic abscess in the upper jaw in the vicinity of the incisors and cuspid which had proved intractable to ordinary treatment His physical condition was much impaired, he was emaciated, his skin was sallow, his cheeks hollow, his conjunctivæ pale, eyes dull, and his lips lacked the color of health His temperature was slightly above normal I could elicit no history of any other illness, recent or otherwise The patient's appearance gave the picture of a toxemia In this case likewise the sharp steel probe revealed a large cavity in the bone, extending from the central incisor to the first molar Oct. 20, 1911, I extracted the cuspid tooth and curetted the bone cavity October 27, he returned to the clinic much improved November 10 his color was normal, his eyes clear and he seemed to be well

Did time permit, additional cases, such as Ludwig's angina, osteomyelitis and other infections and toxemias might be cited, which were due to chronic diseases of the jaws and mouth

A casual ocular examination of the mouth is not always sufficient to demonstrate a blind alveolar abscess, since the tissues overlying the abscess may not always indicate its presence, but by careful scrutiny of the

mouth by the eye, aided by an educated touch, a sharp steel probe and the radiograph, all such infected areas in the jaws may be discovered

Since the internist is not usually familiar with all of the pathology of the mouth, and has not the technic and facilities for examination of the mouth and teeth, if the best results are to be obtained, it is highly important that there should be more cooperation between internists and oral specialists

PYORRHEA ALVEOLARIS

Pyorrhea alveolaris so-called, or as better named by Black phagedenic pericementitis, is a disease strictly of the peridental membrane It is very common, more teeth are lost from it than from caries It is indicated by a progressive destruction of the root membrane of the tooth commencing at the gingival border, generally accompanied by flow of pus and destruction of the alveolar walls Pus appearing at the gum margin is not always a sign of pyorrhea, as will be shown later The clinical picture of pyorrhea simulates, though it is not identical, with conditions brought about by indiscreet use of mercury

Simple calcic inflammation of the gingivæ due to the deposit of salivary or serumal tartar simulates pyorrhea alveolaris and is mistaken for it If it be of the salivary type, the lime deposited is at the gum margins, on the necks of teeth, near the openings of the ducts from the salivary glands If of the serumal type, the lime is deposited just beneath the free margin of the gums, both being productive of pus Serumal deposits are generally found in pyorrhea pockets, but such deposits, when formed, are below the cervical margin of the peridental membrane, and the pus pockets must be there first, while serumal deposits in simple calcic inflammation of the gums are found under the gum margin, but above the occlusal attachment of the membrane In addition to the physical appearances in pyorrhea, in extreme cases, there is always present a peculiar odor which is distinctive These are the chief characteristic differences between pyorrhea and calcic inflammation of the gums The removal of all deposits, in simple calcic gingivitis and calcic pericementitis, with good hygiene afterward, usually suffices for a cure, if the removal has not been too long delayed

The etiology of pyorrhea alveolaris is unknown It has been attributed to gout, tuberculosis, syphilis, bacteria and other causes Bacterial examination has often been resorted to in seeking a clue to the cause of the disease and fungi have been found by Black, Miller and Archovey, which are supposed to bear a causative relation to the disease,[7] but neither has been able to prove the specificity of any one organism

7 Black American System of Dentistry Miller Microorganisms of the Human Mouth Archovey Tr Internat Med Cong, Lond, 1, 862

Independent of the findings of Black, Miller and Archovey, there are indications that pyorrhea is a parasitic disease, since almost always persons coming in close contact with an infected individual, as man and wife, contract it Children of parents having pyorrhea, when they become adults, are very subject to the disease This is by no means a positive indication that the disease is infectious, but is suggestive

The great variety of organisms found in the pockets about teeth affected with pyorrhea alveolaris renders the task of isolation exceedingly difficult

Owing to the temporary closure of pyorrhea pockets about teeth on extension of infection an acute condition is frequently observed It simulates alveolar abscess and is often mistaken for that disease During this stage opportunity is afforded for the greater absorption of bacterial poisons and the escape of bacteria into the lymph and blood streams It is to these causes that we should most commonly expect systemic participation from pyorrhea, rather than from the swallowing of pus liberated from pyorrhea pockets, we cannot, however, ignore the danger to patients from the continual swallowing of this pus True pyorrhea is very intractable to treatment It may be cured if taken in time, and remain cured, provided the cooperation of the patient is elicited to carry out proper hygienic measures afterward

With few exceptions the attitude of the profession toward pyorrhea alveolaris, as in chronic alveolar abscess, has been one of indifference That it should have been supposed that such a disease may exist indefinitely and not be productive of evil is surprising

Osler says [8]

> Of the twenty cases of pernicious anemia which I had under observation in 1909, pyorrhea alveolaris was present in more than half Certain types of nephritis are also believed to be due to oral infection

In the majority of extensive cases of pyorrhea alveolaris, much purulent matter is discharged into the mouth Most of it goes direct to the stomach, while some of the bacteria and their products which have not been discharged into the mouth may pass from the granulating walls of the pus pockets, through the lymph and blood channels, to all parts of the body A question of paramount importance now is What effect do these poisons have on the system and what are then physical indications?

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8 Osler Practice of Medicine, p 440

BACTERIOLOGICAL AND EXPERIMENTAL OBSERVATIONS ON FOCAL INFECTIONS*

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For a number of years observations have been carried on, in connection with the clinic of Dr Frank Billings, at Rush Medical College with reference especially to chronic focal infections and associated systemic disease The more general features and the therapeutic results of this work are presented in the preceding article by Dr Billings Here will be given chiefly some bacteriologic and experimental data derived largely from a study of cases which came under his observation

Some of the first work undertaken had to do with genito-urinary disease and chiefly with infections of the urinary bladder by bacteria of the colon group From the study of many organisms of this variety it has been found that they vary, to a certain extent, both in morphology and in cultural reactions Some are short and plump, others slender and long All are Gram-negative Some grow profusely on ordinary media, others give a scant growth A few varieties were found to grow, at least when first isolated, better under anaerobic conditions than aerobic, none are strictly anaerobes, all produce indol and all acidify milk permanently, and with few exceptions coagulate it after from twenty-four to seventy-two hours They vary much in the rapidity with which they ferment sugars, they produce gas in glucose, saccharose, lactose and mannite By blood-agar plate cultures they may be divided into two distinct groups, hemolytic and non-hemolytic The latter are more common Careful observations of a large number of strains have thus far revealed no change on cultivation with respect to hemolysis, though such changes without doubt have been observed by others Hemolytic and non-hemolytic varieties may show no other differences In most instances the colon bacilli exist pure In two cases, both with hemorrhage from the kidney, *B coli* was mixed, in one case with a Gram-positive coccus which simulated a staphylococcus but which refused to grow in various media under either aerobic or anaerobic conditions, in the other, with a long unbranched thread-like Gram-positive bacillus which grew well but slowly on sugar media and which frequently formed tangled masses This mixed flora was observed repeatedly in both cases for a period of many months without any appreciable alterations

*From the Pathological Laboratory of St Lukes Hospital
*Read before the Chicago Medical Society, Nov 15, 1911

The infections of the bladder and prostate were associated with a variety of clinical conditions, including joint-lesions, neuritis, anemia, pyelitis, etc Often the patients were also neurasthenic Blood-cultures and cultures from joint-fluids, when possible to obtain, have never given positive results This fact inclines one to assume that absorbed toxic substances are responsible for the general symptoms

Some interesting points have appeared in connection with the study of the serum in some of the cases Many do not reveal, at least to any extent, the presence of specific antibodies in the blood In others (four cases) there was distinct evidence that the serum of the patient was less lytic to the homologous organism than normal serum For instance, in one case in which the patient gave a history of urinary infection for many years associated with hemorrhage from the right kidney, the serum had little or no destructive action on the infecting bacillus, whereas normal serum was highly bactericidal The agglutinating power was *nil* and the opsonic content, at first low, became high after treatment with the killed bacillus This loss of specific lytic power of the patients' serum is interesting and deserves further study, especially in chronic infections with organisms of this and related groups The facts in such cases can best be explained by assuming that the microbe, gaining access to the individual, causes specific reactions in the serum, to meet which the microbe specifically adapts itself The microbe thus immunizes itself against an abnormal individual and may be still susceptible to the serum of a normal person This reciprocal adaptation continuing for a long period of time may give rise to profound changes on the part of both microbe and host

In this connection should be mentioned some cases of urinary infection caused by a bacillus growing pure and apparently belonging to the hemophilic group A detailed report of these has been given in a previous article[1] All attempts to grow the bacillus on media other than that containing hemoglobin persistently failed Its growth is scant and better anaerobically than aerobically It is a small, Gram-negative, non-motile bacillus and is distinctly, though not strongly, hemolytic in blood-media It differs from the influenza bacillus in being hemolytic, in not showing any evidence of symbiosis with other germs and also in some of its morphological features In two cases in which it was found the patients suffered from joint trouble at the time or previously, but whether or not it had any causal relationship could not be definitely decided It was non-pathogenic for animals[2]

1 Davis Jour Infect Dis, 1910 vii, 599

2 Since this article was written, C Koch (Ztschr f Geburtsh u Gynakol, 1912, lxix, 634) has described an apparently identical *hemophilic bacillus* which he isolated from two cases of puerperal fever This bacillus appeared in pure culture in the lochia at a time when the fever was at its height and for this reason he believes it was the causative organism

Considerable attention, especially of late, is being given to focal infections about the mouth, nose, throat, teeth, ear and tonsils The last-mentioned have, indeed, for many years been the object of attack and there is little doubt but that they deserve all the blame that they have received It is probably true, however, that the other foci mentioned have not been sufficiently emphasized and I think this is especially the case as regards lesions about the teeth and jaws This subject is discussed in the accompanying article by Dr Gilmer, in which the relation of such lesions to general or systemic conditions, such as anemia, gastro-intestinal disturbances, arthritis, etc, is clearly set forth and its frequency emphasized My own observations along this line have been limited Pyemia, septicemia, meningitis, neuritis, endocarditis, etc, as acute infections originating from alveolar abscesses and infected foci about the teeth, are well-known occurrences Chronic generalized or systemic infections are rarer and less commonly recognized As an illustration of the latter I may mention briefly one rather striking case which came under observation

A young man had been suffering for several weeks with symptoms of severe multiple neuritis associated with some anemia, marked emaciation and slight fever The joints were not involved and physical examination revealed no heart lesion For a long time the patient had been troubled with severe pyorrhea and at the time of examination the gums of the lower jaw were red and swollen, bled easily and on pressure abundant pus exuded from between the teeth and gums Smear and culture examination of this pus revealed, in nearly pure growth, many Gram-positive diplococci resembling pneumococci The colonies produced a green zone on blood-agar and the organism acidified and coagulated milk and fermented inulin A blood-culture made by taking several cubic-centimeters of blood from the vein at the elbow yielded in each of three inoculated culture-tubes a pure growth of the same diplococcus In animals this organism was not highly pathogenic One broth-culture intraperitoneally would kill guinea-pigs in twenty-four to forty-eight hours Two rabbits were inoculated repeatedly with large amounts of culture without manifesting serious or fatal effects Apparently these diplococci are identical with the cocci often found in endocarditis and called endocarditic cocci and they are also probably identical with the diplococcus almost constantly found about the mouth and usually called *Streptococcus viridans* (Schottmuller) I may say, too, that they appear to be the same as the diplococci which I have found at times in the tonsillar crypts especially in cases of endocarditis and which I will discuss later in the paper In this particular case the tonsils were carefully examined and appeared to be normal and no suspicious foci of infection other than the teeth could be held accountable for the condition Unfortunately, the patient did not remain long under observation and the termination is not known

The fact that focal infections of tonsils frequently become general and localize in various parts and organs of the body is a subject which seems to be attracting more attention from year to year Clinically the relation between anginas and certain lesions like acute articular rheumatism and endocarditis has long been suspected and more recently kidney and other lesions have been noted as not infrequent complications of primary tonsillar infections Such complicating lesions may be acute, subacute or chronic About two years ago[3] I published a preliminary statement of some bacteriological and experimental observations with bacteria isolated from tonsils excised from a variety of clinical conditions including chronic and recurrent arthritis, endocarditis, nephritis, recurring tonsillitis, neuritis, etc Since that time many more cases have been studied and some further facts have been noted which seem worthy of record

The clinical features of cases of this type indicate beyond doubt the presence of invading organisms or their toxic products That such cases associated with diseased tonsils may often be influenced favorably by extirpation of these organs has been noted by many clinicians The bacteriology, however, especially of the subacute and chronic systemic conditions, is in many respects incomplete and the literature abounds in general and indefinite statements about the variety of bacteria in the tonsils Work along this line has largely been the examination of swabs and smears made directly from the surface of the tonsils *in situ* This surface is necessarily contaminated by bacteria from the mouth throat, nose, food, etc, and the great variety of bacteria reported to have been found here is thus at least partly explained It is evident, too, that the bacterial flora on the surface may be very different from that in the crypts and some preliminary work on cultures taken from the surfaces and from the crypts of the same tonsils convinced me that this was an important point Consequently, in the study of tonsils, in practically all cases the cultures have been made from the surface and from the crypts of the extirpated tonsils and, in many instances, cultures were also taken from the tonsillar surface before excision and compared with those taken after In order to obtain cultures from the crypts the tonsils, as soon after excision as possible, were incised with a hot knife, thus exposing the depths of the crypts from which these smears and cultures were made In all cases the blood-agar plate method was used

The tonsils, as stated above, came from a variety of clinical conditions which may be conveniently divided into four groups, namely, arthritides, nephritides, cardiac lesions and recurring and chronic tonsillitis The tonsils were usually hypertrophied but not in all cases In some instances in all groups they were normal in size or sometimes, indeed, atrophic

3 Davis Jour Am Med Assn, 1910 lv, 26

Many were submerged and when excised were found to be diseased and much larger than they appeared on simple inspection Their surfaces varied, being at times deep red or purplish-red and irregular, often they were smooth and coarsely lobular In cases with a history of repeated tonsillitis the connective tissue capsule and the septa were thickened and the crypts were often distorted The latter frequently contained small, globular, cheesy, foul-smelling masses In microscopic sections are often seen deep down in the crypts small aggregations of leukocytes in which cocci may be found in suitably stained preparations They are rarely found beneath the epithelium At times the crypts are crowded with pus-cells but this is not common in the chronic cases Plasma-cells are found in abundance beneath the epithelium and especially about the small blood-vessels It should be stated that they are always found in the tonsils after the first few weeks of life regardless of the anatomic condition, but in hypertrophied and diseased tonsils they are as a rule more numerous Giant-cells are sometimes found about cholesterin crystals and débris and should not be mistaken for tuberculous giant-cells Cross-sections of small solid epithelial masses often resemble giant-cells also

The results of culture inoculations from the tonsils of the various groups may be briefly summarized as follows In twenty-eight cases of arthritis hemolytic streptococci were obtained in all and were predominant in twenty-five In many cases the growth was practically pure In two cases the pneumococcus was predominant and in one case the *Streptococcus mucosus* occurred together with a few hemolytic streptococci These cases of arthritis include a variety of joint-lesions ranging from simple joint-pains associated with tonsillitis to severe chronic joint-involvement In some instances the arthritis was deforming in character and associated at times with exudates into the joints The joint-fluids and blood from these cases were invariably sterile

The tonsils from ten cases of nephritis were examined and hemolytic streptococci were found pure or predominant in the crypts in nine In one case a small Gram-positive bacillus in nearly pure growth was found but was not identified These cases of nephritis were subacute or chronic and several patients had developed nephritis shortly after having had colds or tonsillitis Some were mild, others severe, and two were hemorrhagic in character

The tonsils from a series of patients with definite heart lesions were examined following extirpation with interesting results Nearly all were at the time suffering from arthritis or gave histories of having had it in the past and they suffered also from recurrent attacks of tonsillitis Two cases were malignant in character, the others were relatively mild Hemolytic streptococci were found in six and were far more numerous than any other organism In the remaining four, pneumococci appeared

in predominating numbers and in two they were nearly pure In one case of fatal malignant endocarditis with pneumococci in the blood and in the pleural and pericardial exudates, the tonsils were only slightly enlarged but near the base they were very fibrous and in the depths contained small pockets filled with pus-cells and diplococci In the cultures from the crypts pneumococcus-like organisms grew almost pure, there being a few hemolytic streptococci

The extirpated tonsils from sixty-one cases of tonsillar hypertrophy and chronic tonsillitis in which no marked systemic disease existed were examined In fifty, hemolytic streptococci were found in large and usually predominating numbers and often practically in pure growth *Streptococcus mucosus* was found in large numbers in one case and in six the white staphylococcus was more numerous than any other organism In two cases the pneumococcus predominated and were mixed with a few hemolytic streptococci In three instances *B influenzæ* was found in large numbers

The streptococci isolated from the various groups could not be differentiated They were all hemolytic on blood-agar plates and they acidified and nearly always coagulated milk The zone of hemolysis varied considerably, most of the strains producing a wide clear area about the gray colonies, a few strains gave a smaller and a slightly turbid zone and grew usually less luxuriantly They do not differ in their sugar or milk reactions or in their pathogenic properties for animals

Forty-three strains isolated from the tonsillar crypts from the various clinical groups were tested on the following sugars dextrose, lactose mannite, raffinose and inulin Briefly, they all formed acid in dextrose and none in raffinose and inulin All but five fermented lactose, one of these strains coming from a case of arthritis, the other four from cases of recurrent tonsillitis Eleven strains fermented mannite and thirty-two did not The grouping into mannite and non-mannite fermenters has no evident relation whatever to the clinical condition For instance, some streptococci isolated from arthritis cases fermented mannite, others did not and the same is true with reference to the other groups When compared with streptococci from other sources (puerperal fever, erysipelas, empyema, scarlet fever) they show no essential morphological or cultural differences

The organisms referred to in this paper as pneumococci are Gram-positive, lanceolate diplococci and produce a green zone on blood-agar plates In liquid cultures they grow in long chains Some ferment inulin and others do not, all ferment dextrose and lactose and none ferment mannite and raffinose These organisms are commonly called *Streptococcus viridans* (Schottmuller), but I think their more important morphological features and cultural reactions justify one in placing them in the pneumococcus rather than in the streptococcus group Organisms of

this type are found normally on the buccal mucosa and especially on the surface of the tonsils From the many examinations made it appears that they are not commonly found in the crypts except in some cases of endocarditis in which they were found predominant in four of ten cases This is interesting in view of the fact that what appears to be an identical organism is often found in the blood and on the heart-valves in cases of endocarditis More data are desired in order to confirm this point, but it appears that the atrium of infection for these germs in such cases may well be the tonsils These cocci, it may be pointed out, are not the same as those found in the tonsils in acute arthritis, which are apparently typical hemolytic streptococci For this reason, when found in the blood in cases of endocarditis following rheumatism, as often happens, these pneumococci should be looked on as probable secondary invaders localizing in the heart-valves, which were perhaps injured during an earlier infection

Attention should be called to the striking difference that exists between the surface and the crypt flora in tonsils Invariably, on the surface, organisms of the pneumococcus type are found in large and predominating numbers but mixed with a variety of other bacteria Often a few hemolytic streptococci may be found here in the more or less chronic cases In acute infections of the tonsils, however, like diphtheria and acute streptococcic tonsillitis, which primarily involve the surface of the tonsils, naturally the causal organisms will then predominate, though even there the normal pneumococcus-like bacteria may be found in abundance on the culture-plates The presence normally of these surface diplococci so similar to pneumococci is a fact that should always be kept in mind in examining throat cultures Many diagnoses of the so-called pneumococcus throats have been based, no doubt, on the presence of these diplococci The crypts, on the other hand, as shown by the data presented above, contain in most cases hemolytic streptococci in large numbers often nearly pure, and only occasionally, and probably only in certain diseased conditions, do pneumococci invade tonsillar crypts

Strains of organisms from the various clinical groups were inoculated into animals and the results are as follows Seventeen rabbits were inoculated with hemolytic streptococci from the arthritic group, fifteen developed multiple arthritis and one developed acute endocarditis Five strains of pneumococci were tested and in one case mono-articular arthritis appeared, no endocarditis Eight strains of streptococci from the nephritic group injected into rabbits caused arthritis in all Four strains of streptococci from endocarditic cases caused arthritis in all, but no endocarditis, three pneumococcus strains from this group caused endocarditis in two animals but no other lesion Seven strains of hemol-

ytic streptococci from cases of chronic or recurrent tonsillitis caused arthritis in all, four strains of pneumococcus gave negative results The hemolytic streptococci are virulent for guinea-pigs and a strain which had produced arthritis in a rabbit, on intracardiac injection into a monkey (*Macacus rhesus*), caused multiple arthritis The animal died after about two weeks and the cocci were recovered pure from the joints and heart's blood

The arthritis caused in animals by the streptococci is manifested by lameness and swelling of the joints and usually appears from the third to the fifth day after inoculation On the whole, the various strains isolated from the tonsils are quite uniform in their pathogenic properties, a given dose in animals of uniform size usually producing similar results Some of the animals die in the course of one to three weeks but in many the joint-lesions gradually subside and the animal recovers In less severe cases few joints or only one may be involved but usually the arthritis is multiple and in some rabbits almost every joint in the body was attacked including the vertebral joints The carpal joints and the joints of the hind limbs are often the seat of localization and, on the whole, the various joints of the fore and hind limbs are about equally involved In a number of animals the process became chronic, the joints increasing in size with marked destruction of bone and joint-surfaces In one case subluxation occurred after six weeks Chronic joint-abscesses may arise in which streptococci in small numbers may be found in the glairy mucoid or mucopurulent contents and such animals often live for months gradually becoming emaciated and badly crippled but nevertheless appearing quite lively and eating normally Ultimately most of them die but usually without septicemia A few streptococci may be found in the chronic lesions, though in some instances the cultures remained sterile In four animals, following non-fatal injections, the joints simulated a deforming arthritis They became large and exostoses appeared about the end of the bones After several months the deformities in these cases gradualllly, and apparently entirely, disappeared

Post-mortem examination of the animals revealed the fact that not infrequently in the early stages the involvement is peri-articular and often extends to the tendon-sheaths At times, especially in the hind limbs, a tendon-sheath might be involved throughout its entire length and the joint-cavities remain entirely free Microscopic examination of sections through these involved extremities have been made in some of the animals It would appear from the data at hand that the organisms first localize in the subserous structures about the joints, forming small infected foci which later break into the cavities The exudate in the joints early is glairy and mucoid, but soon becomes purulent and contains large numbers of polynuclear cells and streptococci Usually abundant

phagocytosis of this organism in the exudate is noted After a week or longer in some rabbits, but not in all, the exudate may become thick and pasty Streptococci can ordinarily be readily grown from these joint-exudates, but a few exceptions have been noted In one case, in an animal that died on the fifth day with definite arthritis, the cocci could be seen in the leukocytes, but careful cultures on blood-media gave no growth In two other instances, though the involvement of the joint was unmistakable, no organisms grew in the cultures

In the bodies of the inoculated animals careful search was made for other lesions, especially endocarditis In only one instance following inoculation with hemolytic streptococci was a lesion found, vegetative in character, on the tricuspid valve This was not extensive, but was definite and was produced by a strain isolated originally from the crypts of tonsils in a case of multiple arthritis The joints of the animal were also involved, but there was no other localization The organisms were recovered from the heart's blood Pericarditis was not found in any instance

As stated above, in two instances pneumococci produced an endocarditis In one case by intracardiac injection a very extensive mitral endocarditis developed in an animal associated with typical large renal infarcts and septicemia, but without joint-lesions This organism, which fermented inulin and gave the typical green zone on blood-agar, was isolated from the depth of a tonsil from a case of severe multiple arthritis not associated at the time, so far as could be determined clinically, with heart lesions In this case also streptococci were abundant in the tonsils, and on intravenous inoculation into an animal produced arthritis In the second case a definite but less extensive mitral endocarditis was produced by intravenous injection with a pneumococcus from the crypts of the tonsils in a case of recurrent tonsillitis associated with endocarditis From the valvular lesions the organism was recovered pure It did not, even in huge doses, produce arthritis in animals

The mere fact that the various strains of streptococci from tonsils can cause joint-lesions in animals is perhaps in itself not of great significance It has been shown by Cole, Harris, Beattie and others that streptococci from various sources will produce arthritis in animals Indeed, hemolytic streptococci from the normal throat may do so, as I have myself demonstrated It is therefore not surprising that strains from the various clinical groups appear to be identical and behave alike when injected into animals It is possible that the reason why in one individual streptococci causes arthritis, and in another nephritis lies in the varying local susceptibility of the organs of the individual rather than in any peculiar specificity of the infecting cocci

The therapeutic results following tonsil extirpation in this series of cases are, on the whole, distinctly favorable Other observers[4] have obtained similar results in arthritis, nephritis, heart lesions, toxemias, etc The therapeutic results probably furnish the best argument we have, at present at least, in favor of the idea that the cause of these systemic conditions lies in infected tonsils Since in such infected tonsils there are found so often virulent hemolytic streptococci, an organism as we know prone to attack serous surfaces generally, and no evidence, so far as our present technical methods indicate, of any other significant germ, one would seem justified in at least considering this organism a very suspicious etiological agent

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3 Curschmann and Schichhold Munchen med Wchnschr, 1910, lvii, 281

PARASITIC AMEBAS IN THE INTESTINE OF MAN, WITH A STUDY OF THE PROTOZOA FOUND IN THE INTESTINES OF HEALTHY MEN IN THE SOUTHERN UNITED STATES

PRELIMINARY NOTE

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During the past few years, the parasitic protozoa have received a great deal of attention, and now the list of diseases known to be caused by protozoa has become a long one Through all of this, the question has frequently been raised whether the protozoa found in certain diseases were really the cause of the disease or whether they were harmless parasites, their finding being purely coincidental

And nowhere has the question of pathogenicity or non-pathogenicity been raised more frequently than in connection with the parasitic protozoa in the intestine of man Thus, very recently, one worker has studied the stools and the intestinal lesions in a series of cases of amebic dysentery, and on the basis of this study he maintains that amebas do not cause dysentery, but that their presence, even in the ulcers and in the tissues, is purely accidental On the other hand, we have the men who consider that all amebas are, or may become, pathogenic when taken into the intestinal tract of man

The question of the pathogenicity or non-pathogenicity of the flagellata found in the intestine of man is not yet settled to the satisfaction of everybody Early workers had shown conclusively that both pathogenic and non-pathogenic amebas were parasitic in the intestine of man, but it remained for Schaudinn to show how it was possible to distinguish between the two He described a non-pathogenic ameba — *Entamœba coli* — commonly parasitic in the intestine of man, and a pathogenic ameba — *Entamœba histolytica* — found as the cause of dysentery in man His work was accepted, and *E coli* was shown to be a very common parasite in the intestine of healthy men in all parts of the world *E histolytica* was generally the ameba found in dysentery, though there have been occasional reports of *E coli* in amebic dysentery and in liver abscesses

But a later contribution to the study of the amebas parasitic in the intestine of man has not received the attention that it merits in this country Schaudinn was aware that there was a third ameba parasitic

in the intestine of man, but his untimely death left it for his pupil, Viereck, to work out this ameba and to give it the name *Entamœba tetragena* on account of the cyst with four nuclei

Almost at the same time, Hartmann described a dysentery ameba found in the stools of cases of dysentery from Africa, but as he had only vegetative forms of the ameba to work with, he did not see the cysts with four nuclei, and so called his ameba *Entamœba africana* Soon after this, Hartmann had a chance to work over some of Viereck's preparations, and he found that *E africana* was *E tetragena,* so *africana* fell as a species name

E tetragena resembles *E histolytica* in the living state in that when at rest there is a distinct separation into ectoplasm and entoplasm, while it resembles *E coli* in that the nucleus has a distinct nuclear membrane and is plainly visible in the living state

In the vegetative forms of *E tetragena* the nucleus, when properly stained, shows a central caryosome of variable size in which one can see a centriole There is a bright zone around the caryosome, and this zone is marked off from the outer nuclear zone by a granular zone which is the original boundary of the caryosome One often sees two such zones placed one inside the other This distinct appearance of the cyclic change in the caryosome is very characteristic for *E tetragena* Indeed, Hartmann had only vegetative amebas to work with when he described his new ameba, and the most important point was this appearance of the nucleus

But *tetragena* is distinctly marked off from both *coli* and *histolytica* in its cyst formation — the cyst with the dense sausage-shaped chromidia and four nuclei

There is one great source of error Under the conditions that cause *tetragena* to encyst, there are always a great many degenerating amebas in which the nucleus is in all stages of disintegration, and great care is necessary in order not to misinterpret such findings Again, at this time the chromatin is passing off from the nucleus into the plasma to form the chromidia, and such an appearance may easily be mistaken for the nuclear change which takes place in *histolytica* preparatory to budding Last winter, while working in Professor Hartmann's laboratory, I had an opportunity to study the original preparations from a case of amebic dysentery that has been figured and described in some German text-books as a case of *E histolytica* infection Study of some sections freshly stained with iron hematoxylin showed that this was a case of *E tetragena* infection

Strangely enough, the common parasitic ameba of the intestine of the frog (*E ranarum*) resembles *E tetragena* and forms a cyst with four

nuclei, while the common parasitic ameba of the intestine of the mouse (*E muris*) resembles *E coli* very closely and forms a cyst with eight nuclei

Prowazek has recently described a new ameba from Samoa It resembles *coli* very closely, but he finds sufficient differences to make it a new species

Since the description of *E tetragena,* it has been found to be the common dysentery ameba in all parts of the world in which it has been studied, while *E histolytica* is found to be rare as a cause of dysentery Hartmann says of *E tetragena* that "it is far the more frequent of the two dysentery amebas (South America, Africa, India, etc) ," and again, he says of *E histolytica* that "as a rule it is met with only in cases of dysentery from East Asia "

E tetragena has been shown to be a cause of dysentery in China, French Indo-China, the Philippine Islands and Japan (*Entamœba nipponica* is undoubtedly *E tetragena*) , and in the large amount of material which I took to Berlin with me from Manila and Saigon, there was not a case of *E histolytica* infection, all being *tetragena* or *coli* Whether it happened that I did not get the cases of *histolytica* infection in collecting my material in Manila, or whether *histolytica* is rarer as a cause of dysentery in Manila than it was a few years ago, I am unable to say

The great frequency of certain parasitic protozoa in the intestine of healthy men in the tropics is well known, but as is usual, it has not been so well worked out in the southern part of our own country

King studied the prevalence of amebic dysentery in the southern United States, and from the information gathered by him, he decides that it is a rare disease here

E histolytica is generally the parasite found in the cases of amebic dysentery collected by King, though in a few cases *E coli* is reported as the parasite found

E tetragena resembles *E coli* very closely, and undoubtedly the cases of dysentery and liver abscess in which *E coli* is reported as the cause are cases in which *E tetragena* has been mistaken for *E coli* or in which *E coli* was present in addition to the dysentery ameba Again, since *E coli* is a very common parasite in the intestine of healthy persons in tropical and subtropical regions, it is possible that some of these cases were of bacillary or other origin, and the finding of *E coli* was purely coincidental

An interesting case of this nature has occurred in my series here A young woman had a typical case of typhoid fever with positive blood culture and positive Widal She had mild diarrhea throughout her attack of typhoid Her stool was examined during this time and found

to contain numerous vegetative forms and a few incomplete cysts of *E coli,* and literally to swarm with *Trichomonas intestinalis* Since her recovery her bowel movements are normal but cysts of *E coli* and of *T intestinalis* are still present in abundance Another interesting point in this case was that many of the vegetative amebas contained, besides the nucleus, from one to several spherical bodies that might have been mistaken for red blood-cells, except that they were colorless Stained with iron hematoxylin, these bodies proved to be cysts of *T intestinalis* which had been ingested by the amebas

King further found that amebas were not very commonly seen in routine examination of stools, thus in the recent examination of 407 stools of the inmates of the Florida Insane Asylum located at Chattahoochee, amebas were not once demonstrable

In order to add a little to the subject, I have undertaken the routine examination of the stools of the persons living in a settlement near here These people are mostly negroes, and all are living "close to nature"

In the examination, several fresh smears from each stool are examined, and when any protozoa are found, smears are fixed with sublimate-alcohol and stained with iron hematoxylin in the usual way The final identification of the protozoa is made from these stained preparations

In the stools of the first 100 persons examined, I found *E coli* fifty-seven times and *T intestinalis* forty-two times, the two parasites being together twenty-six times Strangely, *Lamblia* was not found at all, and none of the rarer parasitic protozoa — *Prowazekia, Balantidium* or *Nyctotherus* — was found

Different observers have found amebas with or without intestinal ulcers in cases of pellagra, and the question of a relationship between pellagra and parasitic amebas has been raised

I have recently had opportunity to study the stools of two cases of pellagra Amebas were present in the stools of both cases and in both cases they proved to be *E coli Trichomonas intestinalis* was also present in the stools of one case Both of these patients had severe diarrhea — one of them having as many as thirty bowel movements in twenty-four hours The latter patient died but a necropsy was not allowed

My finding in these two cases of pellagra shows that it is not sufficient to find amebas in cases of pellagra, it is necessary to determine what species of ameba is present, by the study of properly fixed and stained specimens, before anything definite can be learned regarding the relationship between pellagra and parasitic amebas

My finding of so high a percentage of infections with *E coli* and *T intestinalis* in healthy men seems to be rather out of accord with the findings of other workers in the southern United States, but from what we know of the finding for tropical and subtropical countries in general,

this high percentage of infections is rather to be expected Whether a larger number of examinations will reduce this percentage, or whether I have merely found a settlement where over half of the people are infected with *E coli,* can only be determined by further work The work will be continued and at a later date I shall hope to give the percentage of infections for a larger series of cases

From the known wide distribution of *E tetragena* as a cause of dysentery, it is very probable that it is the cause of at least a part of the amebic dysentery in the United States, aside from the cases of this infection which are brought from the Philippine Islands and from South America This is rendered all the more probable by the cases collected by King, in which *E coli* is reported as the cause of amebic dysentery and liver abscess, as these cases must have been cases of *E tetragena* infection

SUMMARY

As this is a preliminary note, it is not safe to draw any conclusions until more work is done, but the work may be summed up in a few paragraphs, the points in which seem to be justified

1 *Entamœba coli* and *Trichomonas intestinalis* are common parasites in the intestinal tract of healthy man in this part of Florida

2 The finding of parasitic amebas and flagellates in the intestinal tract in cases of pellagra is purely coincidental The parasites have nothing to do with the disease

3 It is necessary to study stained specimens of every protozoon found in the intestine of man, before determining the species of the protozoon and the question of its connection with disease

4 It is very probable that *E tetragena* is the cause of at least a part of the amebic dysentery in the United States [1]

1 Since writing the above, I have found *E tetragena* in the stools of two colored persons who are suffering from dysentery and who have always lived here I have also received a letter from Captain Craig, in which he informs me that he has found *E tetragena* in material from Illinois, and *E tetragena* has been reported, as a cause of dysentery in the United States, from the Mayos' laboratory at Rochester, Minn

THE PRACTICAL VALUE OF NOGUCHI'S LUETIN REACTION *

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The theoretical conception on which the luetin test is based is one which many investigators must have had in mind before Noguchi made its realization possible by discovering a means of growing the *Treponema pallidum* in pure culture For instance, in an article on "Allergy," von Pirquet had prophesied

> I personally feel quite sure that it will be possible to make the diagnosis of syphilis by cutaneous and subcutaneous inoculation as soon as the syphilis virus can be obtained in pure cultures [1]

In the hope of obtaining a characteristic cutaneous reaction in syphilis various investigators abroad, as well as Schoenberg[2] of New York, inoculated or applied extracts of syphilitic tissues, but the results were often contradictory and always unsatisfactory After many fruitless efforts with various culture mediums, Noguchi finally discovered that when strict anaerobiosis and a medium consisting of serum water to which is added sterile tissue from the rabbit's testicle or kidney are employed, the *Treponema pallidum* can be cultivated in a pure state [3] Noguchi next cultivated anaerobically two strains of the isolated spirochetes, employing for that purpose ascitic fluid and ascitic-fluid-agar, both containing a piece of sterile placenta By grinding in a mortar the agar columns containing innumerable spirochetes, and diluting the resulting paste with the inoculated fluid culture, an emulsion was prepared to which, after it had been heated for one hour to 60 C , 0 5 per cent of phenol was added This emulsion, which Noguchi named luetin, is a slightly viscid, opalescent, sterile fluid which under the dark-field microscope revealed from forty to 100 dead pallida per field Noguchi also prepared for use as a control a sterile carbolized emulsion, exactly the same as the above with the exception that it was not inoculated with the pallidum Both emulsions are to be kept in a refrigerator when not in use

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*Read in the Section on Medicine, New York Academy of Medicine, Dec 19, 1911

1 Von Pirquet, C E Allergy, THE ARCHIVES INT MED , 1911, vii, 288

2 Schoenberg, M J , and Burchill, E A Few Suggestive Experiments for a Cutaneous Reaction for the Diagnosis of Syphilis, New York Med Jour , 1911, xciv, 784

3 Noguchi, Hideyo A Method for the Pure Cultivation of Pathogenic Treponema Pallidum, Jour Exper Med , 1911, xiv, 99

Noguchi now performed inoculation experiments first in syphilitic rabbits and later in human beings The method of preparation of the luetin, the specific cutaneous reaction obtained therewith in suitable cases and the simple technics employed are fully described in Noguchi's recent article [4]

The only one who has thus far had a considerable practical experience with the luetin test, besides Dr Noguchi, is Dr Martin Cohen, who at the outset was supplied with the emulsions and who has performed the test during the past six months in over 200 cases, I wish to express my indebtedness to Dr Cohen for the privilege of observing many of the tests and also for having performed it on a number of my patients

Technic of Intradermatic Injections —Employing a glass syringe with a fine sharp needle, the control emulsion is injected into the cleansed skin of the forearm or arm on one side and the luetin injected at a corresponding site on the opposite side The needle is made to enter the skin just beneath the epidermis and one drop (about 0 1 c c) is injected so as to produce a pale swelling which usually disappears within twenty minutes

Local Appearances —At both sites, in normal individuals and in negative tests, besides the minute trauma due to the needle, there results an erythematous halo which seldom lasts longer than forty-eight hours and has usually receded within twenty-four hours There is no induration and there remains only an ecchymotic area due to the trauma

In positive reactions, on the other hand, the luetin can produce a variety of effects which can be classified as follows

1 Erythema with induration This mildest type of reaction appears in from twenty-four to twenty-eight hours, when it either develops into the next form or undergoes retrogression, when the latter occurs the induration persists for a variable period

2 Papular Form After twenty-four to forty-eight hours the redness and induration increase for three or four days till a papule from 5 to 20 mm in diameter has been formed This papule exhibits areolar telangiectasis and, in case the inflammation now subsides, persistent induration, but it frequently develops into the following form

3 Pustular Form On the fourth or fifth day the papule develops a central area of suppuration with subsequent rupture and extrusion of seropurulent fluid

4 Torpid Form In ten days or more, after the luetin test has apparently been negative, a small papule or pustule develops at the luetin site

Occasionally a rectal temperature of 100 F, slight malaise and mild gastro-intestinal disturbance are observed during the development of the

4 Noguchi, Hideyo A Cutaneous Reaction in Syphilis, Jour Exper Med, 1911, xiv, 557

local inflammation, but as a rule there is no marked constitutional reaction even in markedly positive cases Apparently the test is harmless, it having thus far (Dec 15, 1911) been employed in over 650 cases without any ill-effects

An interesting question is whether the modus operandi of the resulting local response in positive cases is the same with luetin as it is with Old Tuberculin, i e, an anaphylactic phenomenon There is some evidence in favor of this view, on giving successive luetin inoculations in the same individual there is sometimes a flare-up at the site of the original injection, again, the luetin test is generally negative in primary and secondary syphilis On the other hand, the reaction might be due to a pathologically sensitive condition of the skin resulting from previous selective activity of the syphilitic poison, in other words, a condition of cutaneous hypersensitiveness which is not hypersusceptibility in the anaphylactic sense Though Noguchi believes otherwise, he mentions, as a possible explanation of the reaction, this peculiar susceptibility of the skin of syphilitics to traumatic irritation, which has been spoken of by Neisser as *Umstimmung* Noguchi and Cohen have observed independently that occasionally a positive luetin test in syphilis is accompanied by a reaction at the control site, but that the control reaction is always of lesser intensity and is not followed after recession of the inflammation by the characteristic induration which persists at the luetin site for a variable but considerable period

Be this question as it may, the practical results from the two tests which are theoretically analogous are likely to be very different Let us for a moment consider the negative side of the question and compare the results obtained with Old Tuberculin inoculated into the skin of non-tuberculous patients, and the results which Cohen has obtained with luetin injected intradermatically in non-syphilitic cases It is well known that the von Pirquet test is of little practical value in adults for the reason that so many adults have been previously sensitized by some tuberculous infection, from a recent exhaustive study of the tuberculin test at Johns Hopkins, Hamman and Wolman reported 57 per cent of positive von Pirquet reactions in apparently non-tuberculous adults[5] In Cohen's patients, who were clinically and serologically non-syphilitic and who were suffering from minor ailments or various infectious diseases other than syphilis, the luetin tests were regularly negative Noguchi and Cohen have reported that in fifty normal individuals, forty-seven of the luetin tests were absolutely negative and three gave mild and atypical inflammatory responses easily distinguishable from positive reactions Consequently, on the one hand, in non-tuberculous individuals, there were

5 Hamman, L and Wolman, S The Cutaneous and Conjunctival Tuberculin Tests in the Diagnosis of Pulmonary Tuberculosis THE ARCHIVES INT MED, 1909, iii, 307, 1910, vi, 690

57 per cent positive von Pirquet reactions, on the other hand, in non-syphilitic individuals, there were constantly negative luetin tests Apparently, therefore, the test is of considerable negative value

As to the positive value of the test, it has rarely been positive in primary syphilis, inconstantly in secondary syphilis, and seldom in parasyphilitic conditions Fortunately the very stages of syphilis in which such a diagnostic aid is most needed reveal the most marked and constant reactions, namely, hereditary and tertiary syphilis Noguchi reports more than 90 per cent of positive reactions in latent and manifest tertiary syphilis and in congenital syphilis Syphilis being a frequent causative factor in certain eye diseases, notably interstitial keratitis, Cohen[6] performed the test in sixty ophthalmological cases either suspected of being or known to be syphilitic, and compared the results with the clinical evidence and Wassermann reaction He found that the test corresponded in 76⅔ per cent of the cases either with the Wassermann and clinical evidence together or with one of these factors of comparison separately One important observation which Cohen made in the course of these studies was that in a number of cases in which negative Wassermann reactions were presumably the result of recent treatment, the luetin test was positive To what extent the test can be utilized to determine whether a syphilitic infection has been permanently suppressed is not definitely known as yet That the Wassermann reaction is inadequate for this purpose is proved by the following experience

A New York physician whose accidental extragenital infection occurred in 1905 was energetically treated with salicylate injections for four years For two years more the Wassermann test, made at intervals of six months, was always negative, nevertheless a gumma of the tongue developed three months ago, the Wassermann becoming positive at this time On intravenous administration of salvarsan the tumor promptly retrograded, and at the present time, after two months of mercurial treatment, the Wassermann reaction and luetin test are both negative

In another case (W A W) of manifest tertiary syphilis successfully treated with salvarsan and mercury, the Wassermann reaction and luetin test are both negative

In a case (D L D) of virulent syphilitic infection of two years' duration, in which there have been relapses despite prolonged administration of mercury and two injections of salvarsan, the Wassermann test (taken while the patient was under mercurial treatment) is still positive and the luetin test negative

According to Martin Cohen, who has had similar results in several of his own patients, owing to the virulence of the infection anaphylaxis has not become established in the case last mentioned Were the infection to respond to treatment the Wassermann should become negative and the luetin test positive, were the patient to be finally cured, both tests should be negative

6 Cohen, Martin Noguchi's Cutaneous Luetin Reaction and Its Application in Ophthalmology, Arch Ophth , 1912, xli, 8

In conclusion it may be said that if the harmlessness of the procedure and if the results thus far obtained are confirmed by other observers, the reaction is of considerable practical importance and likely to have far-reaching consequences in the future diagnosis of syphilis

SUMMARY

1 The luetin test is a simple harmless procedure consisting essentially of the intradermatic injection of a carbolized emulsion containing dead *Spirochætæ pallidæ*

2 The reaction is negative in normal and non-syphilitic individuals and in various diseases including tuberculosis, pneumonia, typhoid fever, malaria, carcinoma, eczema and psoriasis (Noguchi)

3 The test can already be accepted as of considerable negative value As compared with the von Pirquet reaction, the latter gives more than 50 per cent positive reactions in apparently non-tuberculous adults, whereas the luetin test is constantly negative in both adults and children who are clinically and serologically non-syphilitic

4 The positive value of the test appears to be more limited A positive reaction is rarely obtained in primary syphilis and inconstantly in secondary syphilis Noguchi found the test unsatisfactory in para-syphilitic conditions Whether the negative reactions usually obtained in patients practically cured of syphilis indicate lasting suppression of the disease remains to be determined

In hereditary and tertiary syphilis, however, Noguchi obtained positive reactions in more than 90 per cent of the cases

According to Martin Cohen's studies, in eye affections supposedly syphilitic in etiology, the reaction corresponds with the clinical evidence or with the Wassermann reaction in 76⅔ per cent of cases In a number of Cohen's cases in which negative Wassermann reactions were presumably due to recent treatment, the luetin test was positive

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THE DIAGNOSIS OF COMPLETE ABSENCE OF PANCREATIC SECRETION FROM THE INTESTINE, WITH THE RESULTS OF DIGESTION AND ABSORPTION EXPERIMENTS *

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The absence of pancreatic secretion is due, in the great majority of instances, to obstruction of the pancreatic ducts, rarely to atrophy of the secretive cells It is the purpose of the first part of this article to show that while the diagnosis of many diseases of the pancreas is difficult, that of complete absence of the secretion is usually an easy matter without the use of time-consuming laboratory measures, simply by the inspection and microscopical examination of the feces The second part will deal with my results in digestion and absorption experiments undertaken in cases of exclusion of the pancreatic juice from the intestine, both with and without icterus, with the effect of the administration of pancreatic preparations, and of hydrochloric acid in this condition, with the literature of the subject and the conclusions that may be drawn from such work There will be also a discussion of the Sahli and the Schmidt nucleus tests

I DIAGNOSIS BY EXAMINATION OF THE FECES

The important points in the diagnosis are the following the presence of macroscopic masses of fat in the feces, the bulk of the stools, the finding of microscopic globules of neutral fat in large numbers, and the presence of creatorrhea It will be well to discuss each of these features in detail

1 THE PRESENCE OF MASSES OF FAT VISIBLE TO THE NAKED EYE

The fat may present various appearances, the most striking of which is seen in the so-called "butter" stools, in which considerable amounts of liquid neutral fat which congeal at room temperature and look like butter or the yolk of egg are passed with the stool, but not incorporated in it In two cases I have found small masses resembling pus, which

*Read before the Association of American Physicians, May 9, 1911 That part of the work relating to Case 1 was done under a grant from the Dalton Scholarship Fund

proved on microscopical examination to consist entirely of neutral fat globules A third form, less common and less important, consists of small white crumbly masses These consist, according to von Noorden, of fats with high melting-points They were present in only one of my cases

Macroscopic fat in the feces has long been known as a sign of pancreatic disease, but has usually been considered as of rare occurrence This, however, is very far from being the case, as I pointed out[1] in 1909 No less than five out of the six cases forming the basis of the present article showed macroscopic fat in the feces — three in the shape of butter-stools and the other two as creamy masses For its detection it is necessary only that the stools be examined frequently while the patient is on a diet fairly rich in fat (preferably in the shape of butter, cream, eggs or olive oil), and that the stools when formed should be cut across with a knife, as the fat is sometimes in the interior of the stool when there is none on the outside

The presence of macroscopic fat in the feces must be very nearly pathognomonic of absence of pancreatic juice from the intestine, for I have encountered no case either in the literature or my own experience, in which it was noted without disease of the pancreas In icterus and in diarrhea there may be large amounts of fat in the feces, but it is intimately mingled with the stool, and does not occur, so far as I can ascertain, in the form of separate masses of gross fat

II BULKY STOOLS

The increased size of the movements is a very striking feature Owing to the large amount of fat and protein that escapes digestion, the stools are very large, and usually mushy The total quantity in twenty-four hours reaches 500 or even 1,000 gm, as against 85 gm in the normal person, weighed fresh The weight of the dried stools is also very markedly increased, being 123 gm in twenty-four hours in Case 1 of my series, while the normal amount is about 20 gm There may be also increased frequency, three to five movements in twenty-four hours being not uncommon, but the condition differs from true diarrhea in that the water content is normal or even decreased The mushy consistency is therefore due to the large amount of fat present The color ranges from white or putty-color to a light yellow, and is likewise due to the fat

III THE PRESENCE OF MICROSCOPIC NEUTRAL FAT IN LARGE AMOUNTS

The finding of great numbers of globules of neutral fat, especially if many of them are very large, like those seen in cream, is suggestive of pancreatic disease It is necessary, however, to exclude diarrheal

1 Tileston, W A Review of Recent Work on the Pancreas, Albany Med Ann, 1909, xxx, 619

diseases, which may also show an excess of neutral fat This can be done usually by the lack of a watery character of the discharges and by measuring the time of passage of the stool through the alimentary canal, the time being normal in pancreatic disease (about twenty-four hours), and shortened in diarrhea The time of passage is readily ascertained by noting the time of appearance of the first red stool after the administration of 5 gm of carmin in capsule

In tuberculosis of the peritoneum or of the mesenteric glands there may be interference with the absorption of fat, and the stools may be clay-colored from excess of fat The microscopic appearances of the feces have not been described in a sufficiently large number of these cases to justify definite rules, but in the few cases reported the neutral fat has not been increased

IV CREATORRHEA, OR THE PRESENCE OF UNDIGESTED MUSCLE FIBERS

This condition is very often called azotorrhea, but creatorrhea (κρέας meat) is a more accurate term Normally only a few muscle-fibers are found in the feces, and they are partially digested so that the striations are lost Where the pancreatic juice is deficient it is the rule to find muscle-fibers in great numbers, they are in an undigested state, as shown by the preservation of the cross striations, and may appear in bundles Less frequently there are small bits of meat visible to the naked eye Large numbers of muscle-fibers may be found also in the diarrheal diseases, which are to be excluded in the way indicated in the preceding paragraph The absence of creatorrhea has been reported in a few cases of closure of the pancreatic ducts, but is quite exceptional I have never met with such a case, provided that the patient was willing to eat meat

By these simple examinations, all of which can be carried out by the general practitioner, it is almost always possible to determine the absence of pancreatic juice from the intestine The presence of jaundice does not seriously interfere, for in obstruction of the common duct without involvement of the pancreatic ducts, "butter" stools and creatorrhea are absent, and microscopic neutral fat is not present in large amount The cause of the lack of pancreatic secretion is to be determined from a study of the clinical picture of the case Most frequently it is a carcinoma involving the head of the pancreas or the duodenum in the neighborhood of the papilla of Vater, and here there usually will be jaundice and dilatation of the gall-bladder if the disease has lasted a considerable time Glycosuria is rare If there is a history of attacks of true colic situated in the epigastrium, and there is sugar in the urine, a stone in the duct of Wirsung is the probable diagnosis, provided that gall-stones can be excluded, though the possibility of subacute recurring pancreatitis must be considered I have noted, in a case of stone in the cystic duct with icterus, the presence of small amounts of glucose in the urine, which

disappeared after removal of the gall-stone A history of previous acute hemorrhagic pancreatitis may indicate destruction of the secreting tissue as the cause If icterus is absent or there is only partial obstruction of the bile-duct chronic pancreatitis is the most likely condition It should be borne in mind that emaciation is common in benign diseases of the pancreas, and therefore does not necessarily indicate malignancy especially if there is a history of previous attacks of biliary colic

II DIGESTION AND ABSORPTION

My digestion and absorption experiments were undertaken with the view of studying the total absorption of fat and nitrogen, and the amount of fat-splitting and saponification in cases in which no pancreatic juice reached the intestine I also studied in one such case the effect on absorption of pancreatic preparations, and of large doses of hydrochloric acid and pepsin The chemical examination of the stools without a knowledge of the intake, and particularly the analysis of single specimens, may be very misleading, as a high percentage of fat in the stool may be associated with little fat loss, if the bulk of the excreta is not great It is therefore important to study not only the amount of fat and of fat-splitting in the stool, but also the total absorption of fat, which has not always been done in the past It was not attempted to estimate the amount of carbohydrates in the feces because there is no satisfactory method of doing this, but the stools were tested qualitatively for starch by the iodin method

The food was all weighed or measured In Case 1 an aliquot part of each dish was saved for analysis, and all the aliquot parts were dried together over a water-bath, very carefully mixed, and analyzed for fats, proteins and ash The fat was determined by chloroform extraction in the Soxhlet apparatus, the protein by calculation from the nitrogen content as found by the Kjeldahl method The carbohydrates were determined by difference In the remaining cases the diet consisted of milk and eggs, the fat content of the milk was determined daily by means of the Babcock machine, while the protein was calculated from the average of a number of Kjeldahl determinations The eggs were weighed without the shells and the fat and protein content calculated from Konig's tables

The stools were marked off with charcoal or carmin in the usual way, and the greatest care was taken to guard against error, in fact more than one experiment was repeated because a stool was thrown away by mistake by an attendant or because the demarcation was not satisfactory The stools for the whole period were mixed with alcohol and dried over a water-bath for at least forty-eight hours The feces were then put in an air-tight jar and preserved for analysis At first I attempted to dry the portion intended for analysis to constant weight, but I soon found that it was impossible to do this on account of the large amount of fat, no matter how many days the specimen was dried, there continued to be

a loss of weight For this reason the air-dried feces were used for analysis, and Professor Folin assured me that this was quite as accurate as working with a "pseudo" constant weight The nitrogen was obtained in the usual way by the Kjeldahl method

The fat analysis of the feces was done by the methods used by F Muller[2] in his classic work in this subject, with the exception that chloroform was substituted for ether, as recommended by Rosenfeld[3] One gram of dried feces was extracted for twelve hours with chloroform in the Soxhlet apparatus, the extract evaporated and taken up with ether The ethereal solution was filtered and dried to constant weight, the result giving the amount of neutral fat plus fatty acids The fatty acids were determined by titration with tenth-normal sodium hydroxid, using phenolphthalein as indicator, and were calculated as stearic acid For the soap determinations the old capsule from which the neutral fat and fatty acids had been extracted was boiled for one hour with alcohol containing 3 per cent of hydrochloric acid, and the decoction evaporated to dryness The capsule was then extracted for twelve hours with chloroform, and the extract evaporated The extract and the residue remaining after evaporation of the decoction were then taken up with ether, united, filtered and dried to constant weight, the result was taken as representing the amount of soaps The results obtained by these methods were very satisfactory as regards the neutral fat and fatty acids, but less so in the case of the soaps Here it was often difficult to get the controls to agree, so that the work had to be repeated It is quite doubtful if this method of soap determination is absolutely accurate, and Folin's[4] new method promises better results in this direction Unfortunately it was not available at the time my work was done The figures in the tables represent the average of at least two closely agreeing determinations

REPORTS OF CASES

CASE 1.—*Chronic Pancreatitis With Diabetes, Cirrhosis of the Liver, Ascites, Achylia Gastrica*

Patient.—M M, male, aged 45, a laborer, entered the Massachusetts General Hospital on the service of Dr A K Stone, Oct 5, 1908, hospital No 160,542 The family and past histories were negative He never had attacks of abdominal pain or jaundice Venereal infection was denied He consumed a half-pint of whiskey and two or three quarts of beer over Sunday, but not much during the week The present illness began two years ago with diarrhea, which persisted Along with this there was an occasional pain in the epigastrium of moderate intensity, sharp, shooting, not related to eating The appetite was rather better than formerly, thirst was not increased Seven weeks before admission the

2 Muller, F Untersuchungen uber Icterus, Ztschr f klin Med, 1887, xii, 45

3 Rosenfeld, G Zur Methodik der Fettbestimmung, Centralbl f inn Med, 1900, xxi, 833

4 Folin, O, and Wentworth A H A New Method for the Determination of Fat and Fatty Acids in Feces, Jour Biol Chem 1909, vii, 421

diarrhea increased and he became very weak He had lost about 35 pounds in weight

Physical Examination—Well-developed man, much emaciated, but not cachectic Color good, no jaundice Cheeks red, with distended venules Reflexes normal Chest negative Peripheral arteries moderately thickened The abdomen distended, ascites present The liver was not palpable, the liver dulness normal The spleen was slightly enlarged to percussion, but not palpable The gall-bladder could not be felt On the dorsum of the penis there was a small round scar, no signs of lues elsewhere No edema Temperature 98 F, pulse 80 Blood hemoglobin 80 per cent, leukocytes 5,000, stained specimen normal The urine was usually decreased in amount, at times moderately increased, with a maximum of 2,000 c c It was at times free from sugar, even when the diet was not limited as to carbohydrates At other times it contained varying amounts of sugar, from traces up to 6 per cent, usually from 0 5 to 2 per cent The glycosuria yielded readily to anti-diabetic diet Acetone was rarely and diacetic acid never present *Albumin* was absent

The stools were perfectly characteristic of pancreatic disease, being bulky and frequent, the amount increased even up to 600 gm (fresh weight) in twenty-four hours When there was a normal amount of fat in the diet, the stools were coated with a glistening layer of fat, and frequently large masses of congealed fat like butter lay on the top of the stool Numerous strings of connective tissue were to be seen, looking like cotton twine Microscopically there were great numbers of droplets of neutral fat, fatty acid needles, and numerous striated muscle fibers, well preserved Starch granules not in excess

Examination of the stomach showed absence of free hydrochloric acid, as was suspected from the presence of connective tissue in the feces Fasting contents, 7 c c watery fluid containing mucus but no hydrochloric acid Two examinations were made after the Ewald breakfast and both showed the same condition, viz, a small amount of contents (7 c c) consisting of bread mixed with mucus, and containing no free hydrochloric acid and no lactic acid, total acidity 15 in terms of tenth normal sodium hydroxid (chronic gastritis with hypermotility) An *x* ray examination for pancreatic calculus was negative

Functional Tests—1 A Sahli's glutoid capsule was given at 8 00 a m, October 28, and the urine failed to give the ferric chlorid test at any time during the next forty-eight hours 2 The Schmidt nucleus test was positive, the nuclei staining well throughout the section (time of passage sixteen hours) The Loewi adrenalin test was negative, no mydriasis occurring

Diagnosis—The character of the stools, and particularly the presence of macroscopic fat, pointed to exclusion of the pancreatic juice from the intestine, due either to occlusion of the ducts or to atrophy of the parenchyma of the gland Malignant disease was improbable because of the long duration of the process and the absence of jaundice and cachexia Obstruction of the duct by a calculus could not be excluded, but was improbable on account of the absence of attacks of colic The most likely diagnosis seemed to be chronic pancreatitis, which on account of the glycosuria was probably of the interacinar variety The ascites was probably due to cirrhosis of the liver In addition there was chronic gastritis with achlorhydria

Treatment—The absence of jaundice rendered the case particularly suited for absorption experiments, which were performed accordingly A first period with a mixed diet and no medication was followed by one with large doses of pankreon and calcium carbonate, the diet remaining the same Then it was attempted to study how far the digestion of protein can be aided by the administration of hydrochloric acid, the absence of both pancreatic and gastric juice offering a rare opportunity for such an investigation

The results are tabulated in the accompanying Table 1, which may require a word of explanation The figures under the heading "Loss of Fat" represent the

TABLE 1—CASE 1—CHRONIC PANCREATITIS WITHOUT ICTERUS

	Period	Duration in Days	Diet	Medication	No Stools During Period	Daily Weight Feces Fresh, gm	Daily Weight Feces Dry, gm	Water Content Feces, per cent	Fat in Food, gm	Fat in Feces per cent	Total Fat in Feces, gm	Loss of Fat, per cent	N in Food, gm	N in Feces, gm	Loss of N, per cent	Neutral Fat, per cent	Fatty Acids, per cent	Soaps, per cent	Total Fat Split-ting, Per cent
I	11/ 4/ 7	3	Mixed	None	15	481	123	74	201	39 6	146	72 7	45 7	28 5	62 2	35 8	59	5 2	64
II	11/ 8/10	2	Mixed	Pankreon, Calcium Carb āā 30 g tidpc	5	285	56	80	144 4	35 1	39 8	27 6	33 6	6 85	20 4	15 6	35 1	49 3	84
III	11/22/25	3	Fats restricted	None	10	327	75	77	50 9	20 5	46 3	91	47 4	24 8	53 8	14 1	73 7	12 2	85
IV	11/25/28	3	Fats restricted	Dil HCl 3i Pepsin gr xv —tidpc	10	272	65	76	57 8	20 9	40 8	70 6	46 3	21 4	46 2	14 8	68 9	16 3	85
V	11/28/12/1	3	Fats restricted	Dil HCl 3ii Pepsin gr xv tidpc	6	238	59	75	56 6	19 1	33 8	59 7	50 0	18 4	36 8	12	74 3	13 6	87

proportion of the fat in the food which was recovered from the feces The figures for neutral fats, fatty acids and soaps are percentages of the total fat in the feces, while the total fat-splitting is obtained by adding together the fatty acids and the soaps

The diet in the first two experiments consisted of bread, butter, milk, coffee, soup, meat, eggs, sugar, oatmeal, potato, rice and pudding In the last three experiments it was the same except that butter was omitted and "fat-free" milk was given

The results of the first period are such as are to be expected where the pancreatic juice, so important for the digestion, is absent The great loss of fat (72 7 per cent) and of nitrogen (62 2 per cent) are characteristic The great bulk of the dried stools, the low saponification and the somewhat diminished fat-splitting are also interesting

With the administration of pankreon in the second period a very marked improvement is seen in the absorption of both fat and nitrogen, with a corresponding decrease in the bulk of the stools, and an increase in the fat-splitting The remarkable increase in the soaps is doubtless partly due to the large amounts of calcium administered

In the time intervening between the second and third periods the pankreon was continued, and the patient gained weight at the rate of a pound a day It was soon discovered, however, that his abdomen was swelling rapidly, and the greater part of the retained nitrogen evidently was used to supply ascitic fluid On November 18 he was tapped and eight pints removed

The third period, with a diet poor in fat, was preliminary to the experiments with hydrochloric acid It showed again very poor utilization of nitrogen and fats, 91 per cent of the latter passing out with the feces The soaps were higher than in the first period, but still low, while the fat-splitting was normal

The two periods in which hydrochloric acid was given show a considerable gain in the absorption of nitrogen, the nitrogen loss falling from 53 8 per cent to 36 8 per cent , the improvement, however, is not so marked as that seen in the second period, when pankreon was given The experiment shows, if one is justified in concluding that the pancreatic secretion was absent, that considerable digestion of protein may take place from the action of hydrochloric acid administered by mouth, but that much larger doses are necessary for this purpose (2 drams) than those usually given Of course it is possible that smaller doses may help in achlorhydria by stimulating the pancreas to secretion, where that organ is normal, though Ehrmann[5] has shown, by means of the Volhard method, that the pancreatic secretion is not decreased in simple achlorhydria

5 Ehrmann and Lederer Ueber das Verhalten des Pankreas bei Achylie und Anazidität des Magens, Berl klin Wchnschr , 1908, xlv, 1450, Deutsche med Wchnschr , 1909, xxxv, 879

There was also a considerable drop in the fat loss during the "HCl" periods (from 91 to 60 per cent) but not at all comparable in extent to the effect of pankreon We know that a certain amount of fat can be absorbed independently of the action of the pancreatic juice, and it is not unlikely that an improvement in the digestion and absorption of nitrogen would help the handling of fats In view, however, of the small amount of fat in the diet, it is unnecessary to dwell further on this point

TABLE 2 *—EXAMINATION OF THE URINE (CASE 1)

Date	Amount in 24 hrs, c c	Total N, gm	Dextrose in 24 hrs, gm	Total Chlorin, gm	Indican, Per cent	Ethereal Sulphates, gm	Total Sulphates, gm	Remarks
11/ 4/ 5	410	5 23	6 3		100	0 1340	0 6407	Period 1
11/ 5/ 6	480	6 29	6 2		Trace	0 1775	0 7713	No medication
11/ 6/ 7	540	6 80	7 6		60	0 1706	0 8431	
11/ 8/ 9	610	9 57	17 1		400	0 3601	1 2166	Period 2
11/ 9/10	700	10 55	14 0		200	0 3659	1 5544	Pankreon
11/22/23	575	6 77	0	2 8	40	0 2287	0 8370	Period 3
11/23/24	1125	9 48	0	3 0	80	0 2653	1 0287	No medication
11/24/25	1305	11 50	0	3 4	60	0 3237	1 1582	Low fats
11/25/26	1870	6 29	0	2 8	60	0 1777	0 9070	Period 4
11/26/27	585	7 06	0	3 2	140	0 1686	1 1183	Dil HCl 3j t i d
11/27/28	1215	11 16	0	5 1	100	0 1002	0 7644	
11/28/29	855	8 31	0	3 6	125	0 1415	0 8703	Period 5
11/29/30	825	6 2	0	2 5	80	0 1115	0 5792	Dil HCl 3ij t i d
11/30/ 1	810	8 11	0	3 8	60	0 1910	0 8412	
12/17/18	760	12 55	9 1		50	0 2274	1 1130	Period 6
12/18/19	990	13 20	19 8		250	0 2253	1 3682	Pancreatic ext
12/19/20	1240	14 19	5 0		400	0 0942	1 6488	(Parke, Davis Co) 3 g t i d p c

*The average daily amount of carbohydrates in the diet was as follows in the first period 178 gm, in the second period 198 gm

In a sixth period to test the action of Parke, Davis & Company's extract of pancreas excellent results were being obtained, as shown by the greatly decreased bulk of the stools, but one stool was lost and therefore no analyses of the feces were made

The Urine—The excretion of indican and of ethereal sulphates was studied, because of the fact that these substances are sometimes diminished in pancreatic disease, owing probably to the lessened breaking down of protein to amino-acids The indican was quantitated for each twenty-four-hour period, by Folin's[6] method The figures represent percentages referred to a normal value of 100 It will be

6 Folin, O Approximately Complete Analyses of Thirty Normal Urines Am Jour Physiol, 1905 xiii, 53

seen by referring to the table that there was a moderate decrease of indican on most of the days when no medication was given, and that pancreatic extracts caused a marked increase, up to 400 per cent On the other hand, the daily quantity of ethereal sulphates varied within normal limits

The nitrogen excretion is of interest In the first period (without medication) there is a negative balance of 1 gm in spite of a low excretion With pankreon the nitrogen excretion is greatly increased, but on account of the improved absorption there is a positive balance of 6 7 gm for the two days In the third period (without medication) there was a negative balance of 7 4 gm, while in the two "hydrochloric acid" periods there were positive balances of 0 4 gm and 9 0 gm, respectively

TABLE 3.—NITROGEN BALANCE (CASE 1)

Period	N in food	N in feces	N absorbed	N in urine	N balance
1	45 7	28 5	17 2	18 3	—1 1
2	33 6	6 8	26 8	20 1	+6 7
3	47 4	24 8	22 6	27 7	—5 1
4	46 3	21 4	24 9	24 5	+0 4
5	50 0	18 4	31 6	22 6	+9 0

The glycosuria was moderate at first and yielded readily to antidiabetic diet which, however, could not be adhered to long, on account of the bad digestion of fats The absence of sugar from the urine during Periods 3, 4 and 5 is probably due to undernutrition, as through an oversight the daily ration contained only a little over 1,000 calories Toward the close of December the sugar increased, reaching a maximum of 6 9 per cent and 139 gm in twenty-four hours

The low total chlorin was probably due to the ascites, it was not materially increased by the large doses of hydrochloric acid

Course.—December 24, the patient left the hospital and went home to Lawrence, where he was visited by me, Jan 13 and Feb 4, 1909 Each time he was tapped and about 2,500 c c ascitic fluid withdrawn This showed a specific gravity of 1,011 and an albumin content of 1 per cent, the sediment contained 88 per cent endothelial cells The course of the disease was progressively downward and the patient died March 16, 1909 Autopsy was refused

The remaining five patients in this series all suffered from carcinoma of the head of the pancreas with jaundice

CASE 2.—*Carcinoma of the Head of Pancreas, Obstruction of Common Duct, Metastases in Liver, Ascites, Operation, no Autopsy*

J C, male, Massachusetts General Hospital No 155,682, Irish, plumber, aged 39, entered the hospital Nov 11, 1907, on the service of Dr Fitz, with unimportant family and past history He never had colic or jaundice, had used alcohol to excess for twenty years The present illness began seven weeks before admission with pain in the epigastrium and right hypochondrium and below

the right shoulder-blade, followed a week later by jaundice In three days the skin became intensely yellow and remained so Anorexia, rapid loss of weight (35 pounds) and strength Bowels constipated up to two weeks before admission, then two stools daily Three days before admittance he vomited a quart of brownish-black material, after which the stools became black and foul

Physical Examination—An emaciated, cachectic man with intense jaundice Chest negative, radials and brachials thickened The abdomen showed shifting dulness in the flanks The liver was palpable 5 cm below the ribs, projecting from the liver in the right nipple line there was a smooth, elastic, rounded tumor with pendulum motion (dilated gall-bladder) Spleen not palpable Tenderness in the epigastrium 2 cm to the right of the navel Temperature 101 4 The urine showed no sugar in many examinations, a very slight trace of albumin, bile in large quantity, rare granular casts in the sediment

Blood examination showed red cells 1 9 millions, hemoglogin 40 per cent, leukocytes 6,900 The stools were large, frequent, reddish from admixture with blood In a few days the feces became free from blood, and the patient was put on a milk diet The stools were then clay-colored, large, putty-like On November 17, in the center of such a stool, a mass of creamy material the size of a small cherry was found, on examination it proved to be pure fat On November 27 a similar collection was found in a stool All the specimens examined showed microscopically great numbers of fat droplets, and fatty acid crystals Creatorrhea not tested for (no meat in the diet)

Functional Tests—Sahli's glutoid capsule recovered unaltered from stool twenty-four hours after it was given, no ferric chlorid reaction in urine, control on normal person positive in nine hours Schmidt's nucleus test positive, the nuclei undigested, time of passage twenty-three hours The figures for the absorption experiment will be found in Table 4

Course—The patient lost ground steadily, the pain was severe enough to require opiates, and the melena reappeared on December 5, to continue until death An exploratory laparotomy, December 21, by Dr M H Richardson, revealed a tumor mass in the region of the pancreas, the size of two fists There was a small metastasis in the left lobe of the liver, the gall-bladder was greatly distended but otherwise normal, and there was free fluid in the peritoneal cavity The patient died at home about a week later Autopsy was refused

CASE 3—*Carcinoma of the Head of the Pancreas, Jaundice, Dilatation of the Gall-Bladder, Ascites, Steatorrhea, Creatorrhea, Autopsy*

Patient—T A, Massachusetts General Hospital No 157,382, widow, aged 60, Italian, was admitted March 9, 1908, on the service of Dr W W Gannett The patient had had malaria twenty years ago The present illness began a year before admittance with jaundice and a swelling in the right hypochondrium The icterus disappeared in two weeks, but the mass remained and grew larger Seven months before admittance the jaundice came on again and persisted The abdomen had been swollen for four months Anorexia and nausea were present, but no vomiting, progressive but very gradual loss of weight and strength

Physical Examination—The patient was a fairly developed, emaciated woman with intense jaundice The chest was essentially negative, radial arteries thickened The abdomen was greatly distended with free fluid, after the removal of which the liver could be felt about 8 cm below the costal margin, and below it a smooth, firm, rounded mass moving with respiration, evidently the distended gall-bladder The spleen was readily palpable There was a soft edema of the legs Blood examination showed hemoglobin 70 per cent, red cells 4 1 millions, leukocytes 7,800 The urine was dark, sugar always absent, specific gravity from 1,009 to 1,013, there was a trace of albumin, and much bile, in the sediment, a few casts Ascitic fluid 7,000 c c, specific gravity 1,009, albumin 2 4 per cent, lymphocytes 60 per cent, endothelial cells 40 per cent The stools were small, frequent, gray, some formed others mushy, macroscopic fat absent Bile pigment

was absent The guaiac test was positive Microscopically the fat droplets were usually numerous, sometimes few, with always many fatty acid- and some soap crystals, and many undigested muscle fibers, fairly numerous starch granules The Schmidt meat-ball test showed no digestion of the nuclei, time of passage sixteen hours For the results of the absorption experiment see Table 4

Operation—An exploratory laparotomy, April 14, revealed a mass at the head of the pancreas, ascites, an enlarged liver, and a dilated gall-bladder, from which 450 c c of a foul coffee colored fluid were removed The patient became tremendously emaciated and died May 22, 1908

Autopsy (Dr R Kinnicutt)—There was a hard mass in the head of the pancreas, with marked dilatation of the duct of Wirsung back of it Water could be forced under pressure through both the pancreatic ducts The body and tail of the pancreas were greatly atrophied, so that there was practically no normal gland-tissue The gall-bladder and bile ducts were greatly dilated, the liver weighed 1,878 gm and contained a few small metastases, weight of the spleen 198 gm Microscopical examination showed typical adenocarcinoma, the body and tail of the pancreas were in a state of advanced chronic interstitial pancreatitis, but a few islands of Langerhans remained

CASE 4—*Carcinoma of Head of Pancreas, Jaundice, Dilatation of Gall Bladder, "Butter Stools," Creatorrhea, No Autopsy*

Patient—P B, male, Massachusetts General Hospital No 157,454, Irish, a roofer, aged 64, came in March 13, 1908, on the service of Dr Cutler He had served in the Civil War, and had then malaria repeatedly, dysentery once In Nicaragua, in 1892, he had "Chagres fever" (malaria), followed by jaundice He had been a hard drinker for many years For two years he had done no regular work on account of weakness, and for one year before admittance he had suffered from pain in the pit of the stomach not related to food Five weeks before admittance jaundice suddenly appeared and remained ever since The stools had been clay-colored and the urine dark He had vomited several times lately Progressive loss of weight, from 160 pounds, three years ago, to 121 pounds on entrance

Physical Examination—Patient was well-developed, emaciated and cachectic, he showed intense jaundice with a greenish tinge The chest was negative, marked arteriosclerosis Abdomen The liver dulness was enlarged, extending from the fifth space to 5 cm below the costal border in the right nipple line, the edge sharp, and the surface smooth The dilated gall-bladder was plainly felt, forming a smooth, elastic tumor 8 cm in diameter, which moved with the liver The spleen was readily palpable at the costal margin, and the dulness was increased (old malaria) There was no ascites, temperature normal The blood showed hemoglobin 70 per cent, leukocytes 6,300, no malarial organisms The urine showed no sugar (repeated tests), a very slight trace of albumin, much bile, rare hyaline and fine granular casts

Feces On a mixed diet usually one very large stool daily, of a light brown color, mushy, not formed, microscopically numerous plaques of undigested muscle-fibers, small fat-drops, fatty acid crystals, and fairly numerous starch granules When on a diet of milk and eggs, on several occasions passed at the end of defecation large quantities of liquid fat which on congealing looked like butter or yolk of egg Microscopically these stools consisted of large and small globules of neutral fat, with a smaller number of fatty acid crystals

Functional Tests—After Sahli's glutoid capsule there was no reaction for salol in twenty-four hours, the control gave the salol reaction in the urine in four and one half hours The *absorption* of salol was normal in this patient, for when given in an ordinary gelatine capsule it appeared in the urine in three hours Schmidt's nucleus test showed no digestion of the nuclei, time of passage fourteen hours The results of the absorption experiment are given in Table 4

TABLE 4.—CARCINOMA OF THE PANCREAS, ICTERUS

Case	Date	Duration of Experiment, Days	Diet	No. of Stools in Period	Daily Weight Feces, Fresh, gm	Daily Weight Feces, Dry, gm	Water Content of Feces, per cent	Fat in Food, gm	Fat in Feces, per cent	Total Fat in Feces, gm	Loss of Fat, per cent	N in Food, gm	N in Feces, gm	Loss of N, per cent	Neutral Fat, per cent	Fatty Acids, per cent	Soap, per cent	Total Fat Splitting, per cent
2 J C	11/23/25	2	Milk 3,425 c c	3	309	77	75	125	61 4	94 6	75 6	19 2	3 8	19 8	13 8	69 5	16 6	86 1
3 T A	3/19/22	3	Milk 5,035 c c	8		73		175		119	68	28 2						
4 P B	3/28/30	2	Milk 4,140 c c 6 eggs	3	225	70	69	184	69 1	96 7	52 6	29 7	4 3	14 5	49 4	44 7	5 9*	50 6
5 N C	4/19/22	2½	Milk 5,620 c c 7 eggs	7		84		239	51 4	109	45 6	39 5	8 35	21 1	17 6	70 9	11 5	82 4
6 J C	4/18/21	3	Milk 4,675 c c	10		43		162	61 2	79 6	49 1				26 3	67 6	6	73 6

*One determination only

Course—The patient suffered from considerable pain in the epigastrium, requiring morphin almost daily He lost steadily and died April 25, 1908 During the last two days he vomited fluid containing bile, but no blood, probably the growth in ulcerating had opened the common bile-duct, for there had been complete acholia previously Autopsy was refused

CASE 5—*Carcinoma of the Head of Pancreas, Jaundice, Dilatation of Gall-Bladder, Steatorrhea, Creatorrhea, Cholecyst-Enterostomy Autopsy*

Patient—N C, male, Massachusetts General Hospital No 157,830, Italian, brick-layer, aged 52, entered the hospital April 7, 1908, on the service of Dr E G Cutler Past history was negative, patient had never been jaundiced before, alcohol moderately For three months he had had pain in the epigastrium and right hypochondrium, not severe, occasionally radiating to the right back, worse after eating True colic had been absent Jaundice had been noticed for the past six weeks, with clay stools The appetite was good, no vomiting, constipation present

Physical Examination—Well developed, poorly nourished man, deeply jaundiced The chest was negative The liver was moderately enlarged, reaching 4 cm below the ribs in the nipple-line, at one examination the gall-bladder was distinctly felt, about the size of a hen's egg The spleen was not palpable and there was no ascites The blood showed hemoglobin 90 per cent, leukocytes 2,700 The urine varied in amount from 1,000 to 2,100 c c, sugar was always absent, albumin, slightest possible trace, much bile, no casts Stomach examination The size, position, motility, and secretion were all normal On a mixed diet the stools were formed and clay colored, microscopically there was an abundance of undigested muscle fibers, and of fat, the guaiac reaction was positive on two occasions, usually negative On a diet of milk and eggs the stools were white, glistening, and mushy On one occasion only there was found on the top of the stool some cream like stuff, which was found to consist chiefly of large oil drops Microscopically there was always a considerable number of small and sometimes large neutral fat droplets, many fatty acid crystals, no starch

Functional Tests—Sahli's glutoid capsule not given The Schmidt meat balls were recovered after fourteen hours, and showed no digestion of the nuclei For the results of the absorption experiment see Table 4

Course—April 23, Dr Mumford opened the abdomen, and found a mass in the region of the pancreas, and a distended gall-bladder the size of a small orange He performed cholecystocolostomy The patient died three days later The *autopsy* (Dr J H Wright) showed adenocarcinoma of the head of the pancreas, with advanced chronic interstitial pancreatitis of the interlobular type involving the rest of the organ, the islands of Langerhans were preserved, but the acini were almost entirely replaced by fibrous tissue The duct of Wirsung was compressed by the tumor, and greatly dilated behind it, the duct of Santorini admitted a fine probe for a few millimeters only There were metastases in the liver and in an abdominal lymph-node

CASE 6—*Carcinoma of the Head of Pancreas, Jaundice, Dilatation of the Gall-Bladder, "Butter" Stools, Creatorrhea, Operation, Cholecystocolostomy, Autopsy*

Patient—J C, a widow, born in Nova Scotia, aged 55, Massachusetts General Hospital No 157,898, was admitted April 12, 1908, on the service of Dr W W Gannett The patient had "sciatic rheumatism" two years ago, nine children, no miscarriages She drank eight cups of tea a day, no alcohol The present illness began six months previous to admittance, following a big dose of salts She had diarrhea for a week and felt poorly for a month, was then well till Christmas, since when she had anorexia and constant indigestion, with pain in epigastrium after food, but no vomiting Three weeks before admittance she first noticed a yellow color of the skin, which gradually became more intense The bowels were constipated She had lost a good deal of weight, from 185 pounds last summer to 146 pounds on entrance

Physical Examination—The patient was intensely jaundiced and moderately emaciated The abdomen showed liver dulness from the sixth rib to 2 cm below the costal margin, the edge of the liver was palpable, the gall-bladder not felt There was no enlargement of the spleen The blood showed hemoglobin 65 per cent, red cells 5 2 millions, leukocytes 5,600 The urine varied in amount from 500 to 1,200 c c , specific gravity 1.010, sugar absent, albumin a slight trace, bile present, in the sediment, numerous hyaline and granular casts, once epithelial casts Stomach examinations showed no fasting contents, no contents removable after Ewald breakfast, normal size and position The stools were clay-colored, sometimes formed, sometimes mushy Twice, although at the time on a diet with restricted fats, there were pools of congealed fat on the top of the stools, completely soluble in ether Microscopically there were enormous numbers of droplets of neutral fat, many of them large, with relatively few fatty acid crystals and many undigested muscle fibers The guaiac test for blood was negative Schmidt's meat-ball recovered after twenty hours, showed no digestion of the nuclei For the results of the absorption experiment see Table 4

Course—April 28, Dr Scudder opened the abdomen and found a nodular mass involving the head of the pancreas, and a greatly distended gall-bladder, from which about a pint of colorless mucous fluid was removed, also a single gall-stone the size of an olive The cystic and common ducts were free Cholecystocolostomy was performed The patient died April 30 At the *autopsy* (Dr Oscar Richardson) there was found an adenocarcinoma of the head of the pancreas, compressing both the duct of Wirsung and the common bile duct The rest of the pancreas showed marked chronic interstitial pancreatitis with atrophy of the parenchyma and dilatation of the duct of Wirsung The microscopic examination confirmed the diagnosis

THE DIGESTION AND ABSORPTION OF FATS IN THE ABSENCE OF THE PANCREATIC JUICE

The importance of the pancreatic juice for the absorption of fat was first shown experimentally by Claude Bernard,[7] who observed large amounts of fat in the feces after destruction of the pancreas by injections of oil into the ducts The next important work on the subject was done by Abelmann,[8] under Minkowski's direction After total extirpation of the pancreas in dogs he found that non-emulsified fats were not absorbed at all, and emulsified fats only to the extent of 30 per cent The amount of fat-splitting was inconstant, varying from 30 to 85 per cent Later observers studied the effects of ligation of the pancreatic ducts, and arrived at conflicting conclusions, some even finding no disturbance of fat absorption at all For this reason it was assumed that the external secretion of the pancreas after ligation of the ducts might be absorbed and enter the circulation through the lymphatics, and in this roundabout manner get back to the intestine again and be available for digestion That this theory is erroneous was shown by Hess,[9] who demonstrated that in the dog there are always two pancreatic ducts, usually three, and some-

7 Bernard, C Mémoire sur le pancréas, etc , Paris, 1856, p 99

8 Abelmann Ueber die Ausnutzung der Nahrungstoffe nach Pankreasextirpation, Dissert Dorpat, 1890

9 Hess, O Experimentelle Beitrage zur Anatomie und Pathologie des Pankreas, Med Naturwissenschaftl Arch , 1907, 1, 161

times four In his experiments the ligation of two ducts never caused marked disturbance of fat absorption, because some pancreatic secretion still entered the intestine through the third duct After three ducts had been tied off, however, he found that only 5 per cent of the fat of the food was absorbed The previous observers simply had not ligated all the ducts Somewhat later, J H Pratt[10] demonstrated the paramount importance of the pancreatic juice, using a method devised by F T Murphy, which completely isolated the pancreas from the intestine In all of his animal experiments, Pratt found a marked impairment of fat absorption, 67 per cent of the intake being recovered from the feces The fat-splitting was normal and the amount of soap in the feces inconstant As in human beings with a like condition, the stools were massive, and fat visible to the naked eye was present

With regard to the effect on the absorption of nitrogen, Abelmann, Hess and Pratt obtained very similar results, a nitrogen loss in the neighborhood of 55 per cent being observed

Before taking up the question of the effect of the exclusion of pancreatic juice from the intestine in man, it will be best to state the normal figures From 90 to 95 per cent of the fat of the food is absorbed under physiological conditions Of the fecal fat, approximately 20 per cent is in the form of neutral fat, and 80 per cent is split, the soap and fatty acids are about equal in amount, i e, about 40 per cent each

Since some of the cases investigated have been complicated with icterus, it is necessary to discuss the effect of the exclusion of bile *per se* on the absorption The importance of bile for the absorption of fat was first shown for man by F Muller,[2] who found in obstruction of the common bile-duct with patent pancreatic ducts an average loss of fat amounting to 67 per cent of the intake The fat-splitting, however, was normal and the nitrogen loss only slightly above the normal, averaging 11 per cent Brugsch,[11] however, found much less disturbance with fat absorption, averaging 45 per cent fat loss, and suggested as a reason for the discrepancy that in Muller's cases complicating diseases of the alimentary system (cirrhosis of the liver, carcinoma) had a deteriorating influence on fat absorption This seems quite likely, for Schmidt[12] found in two cases of complete obstruction of the bile-duct only 27 per cent fat loss, and Albu,[13] in a patient with biliary fistula and no bile in the stools, but who was otherwise in perfect health, a fat loss averaging

10 Pratt, J H, Lamson, P D, and Marks, H K The Effect of Excluding Pancreatic Juice from the Intestine, Tr Assn Am Phys, 1909, xxiv, 266

11 Brugsch, T Der Einfluss des Pankreassaftes und der Galle auf die Darmverdauung, Ztschr f klin Med, 1906, lviii, 518

12 Schmidt, A, and Strasburger, J Die Faeces des Menschen, Ed 3, 1910, p 171

13 Albu, A Zur Physiologie und Pathologie der Gallensecretion, Berl klin Wchnschr, 1900, xxxvii, 892

38 per cent These wide variations certainly call for caution in the interpretation of the fat loss in cases with icterus

Muller,[2] in a case of atrophy of the pancreas with obstruction of the duct of Wirsung by calculi, found on analysis of a single stool no increase in the percentage of total fat, but a marked diminution of the fat-splitting and a great decrease in the soaps He concluded that the absence of the pancreatic juice does not interfere with the absorption of fat, but does hinder the fat-splitting It should be noted, however, that he did not perform absorption experiments and that the state of the duct of Santorini at the autopsy is not mentioned so that it is possible that some secretion did reach the intestine

Later observers, with the exception of Keuthe,[18] have all found that absence of the pancreatic juice without icterus causes a marked diminution of fat absorption Altogether fifteen cases with absorption experiments are available, viz , those of Brugsch[11] (three cases), Deucher[14] (two cases), Ehrmann,[15] Gigon,[16] Glaessner and Sigel[17] (also studied by Keuthe[18]), Hailey,[19] Masuyama and Schild,[20] Salomon,[21] Ury and Alexander,[22] Weintraud[23] (two cases) and Case 1 of my series The average loss of fat was 55 per cent, the maximum 83 per cent If one excludes Weintraud's cases, in which the diagnosis of total exclusion of the pancreatic juice is probable but not certain, the average rises to 60 per cent

The cases of Gigon[16] and Keuthe[18] require a separate consideration on account of the slight degree to which the fat absorption was impaired In Gigon's patient, a diabetic, the sudden appearance of bulky stools pointed to blocking of the ducts by calculi The average fat loss was only 29 per cent, the minimum 19 per cent At the autopsy seven weeks later

14 Deucher, P Stoffwechseluntersuchungen bei Verschluss des Ductus Pancreaticus, Knorr Bl f schweiz Aerzte, 1898, xxviii, 321, 361

15 Ehrmann, R Stoffwechsel- und Stuhluntersuchungen in einem Fall von chronischer Pankreatitis, Ztschr f klin Med, 1910, lxix, 319

16 Gigon, A Stoffwechselversuch an einem Falle von Pankreasdiabetes, Ztschr f klin Med 1907, lxiii, 420

17 Glaessner and Sigel Organotherapeutische Versuche bei Pankreaserkrankung, Berl klin Wchnschr, 1904, xli, 440

18 Keuthe, W Ein Fall von Pankreasatrophie, Berl klin Wchnschr, 1909, xlvi, 47

19 Harley, V Absorption and Metabolism in Obstruction of the Pancreatic Duct, Jour Path and Bacteriol, 1895, iii, 245

20 Masuyama and Schild Ueber die Behandlung der diabetischen Steatorrhea mit Pankreasprapaiate Ztschr f physik u diat Therap, 1900, iii, 451

21 Salomon, H Organotherapie der Fettstuhle bei Pankreaserkrankung, Berl klin Wchnschr, 1902, xxxix, 45

22 Ury and Alexander Ueber abnorme Stuhlbefunde bei Pankreaserkrankungen, Deutsch med Wchnschr 1904, xxx, 1311 and 1345

23 Weintraud Die Bedeutung des quantitativen Stoffwechselversuches fur die Diagnostik innerer Krankheiten, insbesondere von Pankreaserkrankungen Die Heilkunde, 1898-99, iii, 67

both pancreatic ducts were found obstructed by calculi, and dilated behind the obstruction, so that it is reasonable to suppose that no pancreatic juice got into the intestine It is conceivable that at the time of the absorption experiments only one duct was obstructed, and that the other became plugged shortly before death, but in view of the fact that both ducts were dilated, this explanation seems somewhat strained

Keuthe's case is still more remarkable This patient was first investigated by Glaessner and Sigel, who found a fat loss of 57 per cent Five years later the patient came under Keuthe's observation, and showed on a Schmidt diet a fat loss of only 10 per cent, i e, at the upper limits of the normal The Sahli, Schmidt, and Schlecht trypsin tests all pointed toward the absence of pancreatic juice Icterus was absent The stool was formed, clay-colored, and microscopically showed an excess of neutral fat and undigested muscle-fibers Urobilin was present The nitrogen was not estimated At the autopsy the pancreas was so small that it was located with difficulty, and the ducts could not be found at all, not even with the microscope The microscopical examination showed chronic interstitial pancreatitis, with only traces of normal parenchyma remaining

There are several possible explanations of the normal utilization of fat in this case First, it is conceivable that through some compensatory mechanism, the fat-splitting ferments of the stomach and intestine, together with the bile, were able to bring about a normal absorption of fat Such a phenomenon, however, has not been shown to occur in other cases in human beings, nor in the animal experiments Second, there might have been an error in the fat determinations This is unlikely because the error would have to be tremendous to explain the results Third, it is possible that the atrophic pancreas, or an accessory pancreas which was overlooked at the autopsy, produced sufficient steapsin to digest most of the fat This explanation seems to me the most plausible But in any case, the fact remains that it is possible to have normal fat absorption with almost total destruction of the pancreas

With regard to the fat-splitting in the absence of pancreatic juice there has been considerable difference of opinion Normally 60 to 80 per cent of the fecal fat is split, that is to say, is in the form of fatty acids and soaps Schmidt[12] found an average of 60 per cent in three normal persons, other observers about 80 per cent Muller[2] found a marked decrease in the fat-splitting, and Katz,[24] who did only percentage analyses of single stools, went so far as to say that fat-splitting was the most important feature from the point of view of diagnosis, and that values for split fats below 70 per cent (!) signified a diminution or absence of

24 Katz, A Semiotische Bedeutung der Zusammensetzung des Kothfettes Wien med Wchnschr, 1899, xlix, 153, 214 and 266

the pancreatic juice In Case 4 of my series only 51 per cent of the fat was split, in Case 1, (Period I) 64 per cent, in the others the fat-splitting was normal Speaking in general, the fat-splitting has been found in the majority of instances (Brugsch, Meyer, Deucher, Harley, Tileston, etc), either normal or only slightly diminished, as has been the case also in the animal experiments A normal fat-splitting therefore does not speak against pancreatic achylia, while a marked reduction probably speaks in favor of it Since the amount of fat-splitting by intestinal bacteria is small (15 per cent, Muller[2]) the function is probably performed in the absence of pancreatic secretion by the fat-splitting ferment of the intestine described by Boldireff,[25] and by the steapsin of the gastric juice

The saponification in the condition under discussion is almost invariably considerably diminished below the normal percentage of 40 per cent Thus Deucher found only 7 per cent and 9 5 per cent, Meyer 6 to 9 per cent, Ehrmann 15 per cent, Brugsch 8 to 33 per cent, and Tileston (Case 1) 5 per cent The reason for the reduction probably lies in the small amount of alkali available in the intestine Zoja[26] attached considerable importance to a diminution of the soaps, but since this condition also obtains in other diseases the amount of saponification has no diagnostic value, except in the negative sense that an excess of soaps over fatty acids renders pancreatic achylia improbable

If bile as well as pancreatic juice is excluded from the intestine, as occurs frequently in cancer of the head of the pancreas and cases in which a calculus becomes impacted in the duodenal papilla, the disturbance of fat absorption is apparently greater than where the pancreatic duct alone is obstructed Thus, Brugsch[11] found for obstruction of the bile-duct alone a fat loss averaging 45 per cent, for obstruction of the pancreatic ducts alone 65 per cent, and for the exclusion of both bile and pancreatic juice 87 per cent Meyer,[27] in a case of cancer of the pancreas with compression of the bile and pancreatic ducts, found a fat loss varying from 69 to 77 per cent with the patient on a diet of meat, eggs, bread and potatoes while it was only 62 per cent on a diet of milk, butter and bread My figures in five such cases (all but one verified by either operation or autopsy) were still lower, ranging from 46 to 76 per cent, and averaging 58 per cent It seems possible that the difference is due to the diet, for my patients were on a diet consisting exclusively of milk and eggs, and Abelmann showed that in dogs after extirpation of the pancreas emulsified fats were better absorbed than were non-emulsified fats Brugsch, to

25 Boldireff, V N Das Fettspaltende Ferment des Darmsaftes, Centralbl f Physiol, 1904, xviii, 460

26 Zoja, R Note cliniche sull'assorbimento del grasso, Morgagni, 1899, xli, 1, abstract in Centralbl f inn Med, 1899, xx, 1261

27 Meyer, E Stoffwechsel bei Pankreaserkrankung und dessen Beeinflussung durch Opium u Pankreaszufuhr, Ztschr f exper Path u Therap, 1906, iii, 58

be sure, on the basis of a single case, makes the statement that in the case of pancreatic disease in man emulsified fats are *not* better absorbed than other fats This point is worthy of further investigation. To sum up, then, pancreatic achylia with icterus usually is accompanied by a greater fat loss than is simple icterus, but exceptionally, as in Muller's cases, the fat loss in the latter way may be so high as to cause diagnostic difficulties

The complication of pancreatic disease with jaundice apparently does not alter the amount of fat-splitting and saponification

THE NITROGEN LOSS

Normally from 5 to 10 per cent of the nitrogen in the food can be recovered from the feces Part of this is derived not from the food but from the intestinal secretions and the bacteria In experimental exclusion of the pancreatic juice there is a large nitrogen loss averaging about 55 per cent The nitrogen loss in animals is thus somewhat less than the fat loss, and this is probably due to compensatory action on the part of the gastric and intestinal proteolytic ferments In the human subjects with deficiency of the pancreatic juice varying degrees of disturbance with the utilization of nitrogen have been observed, Deucher's first case showing only 19 per cent nitrogen loss and Salomon's 87 per cent , in my first case it was 62 per cent The average nitrogen loss in nine cases without icterus was 39 per cent Brugsch therefore puts the figure considerably too low when he states that the average nitrogen loss is from 20 to 25 per cent The explanation of this is that he has excluded cases without autopsy, while I have taken in those cases in the literature which showed "butter" stools and creatorrhea and often glycosuria, in other words, cases in which the diagnosis of pancreatic disease was certain even in the absence of autopsy In simple icterus (Muller, Brugsch) the average nitrogen loss is 11 per cent, or only slightly above the normal

In three cases complicated with icterus, Brugsch found an average nitrogen loss of 34 per cent , in one of them on a milk diet the nitrogen loss was 5 4 per cent less than it was on a diet containing meat In my three cases with icterus in which the nitrogen loss was determined it varied from 14 5 per cent to 20 per cent, averaging 18 5 per cent As previously stated, these patients got only milk and eggs, which may account for the lower figures For erepsin can attack casein, *though it is* powerless against the other native proteins, and it is obvious that egg albumin will be more readily broken up than meat Gigon[16] found that on the addition of 80 gm of casein to the diet the nitrogen loss fell from 24 to 12 per cent and Muller[2] in a patient with probable pancreatic disease found a nitrogen loss of 28 per cent on a meat diet, while on a milk diet the nitrogen loss was less than half as great (13 per cent)

THE DIGESTION AND ABSORPTION OF CARBOHYDRATES IN PANCREATIC DISEASE

Since there are no satisfactory methods of quantitating the carbohydrates in the feces, we are limited to qualitative tests for unaltered starch These have shown, as a rule, no marked excess of undigested starch In none of my four patients who were on a diet containing starch was there a striking increase in the number of undigested starch granules in the feces Similar statements are to be found in the literature It seems probable, therefore, that in the absence of the pancreatic secretion the other diastatic ferments are sufficient for the digestion of the starch in the food, and its absorption after conversion to dextrose is certain to occur

THE EFFECT OF OPOTHERAPY IN PANCREATIC DISEASE

There can be no question that the administration of raw pancreas, and to a somewhat less degree that of pancreatic extracts, can to a considerable extent supplant the action of the pancreatic juice, with regard to the absorption both of fat and of nitrogen My experiments in Case 1 clearly show this, and they are in accord with a few exact absorption experiments made by others Thus Masuyama and Schild[20] at von Noorden's clinic found the fat loss decreased from 63 per cent to 36 per cent on the administration of raw pancreas In Salomon's[21] exhaustively studied case raw pancreas diminished the fat loss from 52 to 20 per cent and the nitrogen loss from 70 to 22 per cent, and pancreatin (Rhenania) was equally effective, reducing the fat loss from 53 to 17 per cent and the nitrogen loss from 87 to 25 per cent Six months later pankreon gave similar results The results of Ury and Alexander[22] were less striking, pankreon lowering the fat loss from 72 to 58 per cent and the nitrogen loss from 40 to 27 per cent Gigon[16] noted a marked improvement with pankreon, but the effect soon wore off Later, with larger doses, the absorption again improved, but only temporarily Other observers do not appear to have found pancreatic extracts to lose their effect after continued administration In Meyer's[27] case treated with 3 gm pankreon daily the fat loss fell from 74 to 35 per cent and the nitrogen loss from 64 per cent to 38 per cent The administration of opium likewise caused a moderate improvement in absorption, probably by delaying peristalsis Ehrmann[15] used massive doses of pancreatin (25 gm daily) on account of the normal gastric secretion in his case, and reduced the fat loss from 50 to 17 per cent and the nitrogen loss from 43 to 17 per cent

The effect of adding alkali to the pancreatic preparation was studied by Glaessner and Sigel[17] Pankreon alone (5 gm daily) had no good effect on the fat absorption, and only a trifling one on that of nitrogen. When 30 gm of sodium bicarbonate was added to the pankreon, the fat loss was diminished from 56 to 41 per cent and the nitrogen loss from

45 5 to 42 per cent Pancreatin Rhenania (1 25 gm daily) when given alone reduced the fat loss by 28 per cent and the nitrogen loss by 4 5 per cent, while pancreatin with sodium bicarbonate was somewhat more efficacious, reducing the fat loss by 32 per cent and the nitrogen loss by 9 per cent It will be noted that the effect of pancreatic preparations was much less marked than that found by other observers, especially in regard to the nitrogen Whether this is to be attributed to the relatively small doses or to some peculiarity of the case it is hard to say The work of these authors renders it advisable to give some alkali with the pancreatic preparation

All observers have found after the administration of pancreatic extracts a well-marked increase in the fat-splitting and in the saponification, thus in my first case the fat-splitting was increased 31 per cent and the saponification nine-fold

With regard to the selection of the preparation to be used, the raw pancreas is sometimes more efficacious, but is likely to become distasteful to the patient, may cause diarrhea, and is troublesome to obtain Pankreon, a combination of pancreatic extract with tannic acid, has been highly recommended on the ground that it is not acted on by the gastric juice, it does not seem to be superior to other active preparations of pancreas

DIAGNOSTIC CONCLUSIONS TO BE DRAWN FROM ABSORPTION EXPERIMENTS

1 In cases without icterus Here a loss of fat of 30 per cent or over speaks very strongly in favor of pancreatic disease It should be emphasized however, that if the stools are watery no conclusion can be drawn with regard to the pancreatic secretion, for simple diarrhea or chronic catarrhal conditions of the intestine, especially in children, may be accompanied by a very considerable loss of fat In case of doubt the water content will be of assistance, being normal or decreased in pancreatic disease and increased in diarrhea If the stools are not watery, but mushy or formed, as is usually the case in pancreatic disease, it is only necessary to exclude a few intestinal diseases in which there may be interference with the absorption of fat These are tuberculosis and amyloid of the intestine, tuberculous peritonitis and tuberculosis of the mesenteric lymph-nodes It should be also borne in mind that some individuals, as Edsall[28] has shown, have an intolerance for fat, and if a certain moderate amount of fat in the diet be exceeded, will show a considerable loss of fat with the stools Such persons, however, are healthy in other respects, and if the fat in the diet be diminished the abnormal loss of fat disappears, while in pancreatic disease there will be

28 Edsall, D L Intolerance of Fats, Boston Med Surg Jour, 1906, clv, 763

a marked loss of fat even when the fats are greatly restricted (see Period 3 in Case 1)

A marked reduction of the fat-splitting is also in favor of disease of the pancreas, but since most cases show normal fat-splitting, this point will not often be helpful in diagnosis From diminished saponification no positive conclusions can be drawn The most we can say is, with Brugsch, that a percentage of soaps in excess over the fatty acids is against the diagnosis of pancreatic disease, provided that pancreatic extracts or large amounts of alkali are not being administered

2 In cases with icterus, according to Brugsch, a fat loss below 60 per cent excludes disease of the pancreas, while a loss over 60 per cent makes pancreatic disease probable In view of my results, I should be inclined to place the figure a little lower, say at 50 per cent, especially if the patient is on a milk diet It is certainly exceptional to have in simple icterus a fat loss of over 50 per cent

With regard to nitrogen, it may be said that a nitrogen loss of over 30 per cent points strongly to disease of the pancreas, whether icterus is present or not, provided that the above-mentioned intestinal diseases are excluded, while figures below this are consistent with pancreatic achylia but are also encountered in other diseases Since in pancreatic disease the loss of nitrogen is less on a milk than on a meat diet, it will be well to give meat during absorption tests The diagnostic value of the nitrogen loss is especially marked in cases with icterus, for in simple exclusion of bile from the intestine the nitrogen loss never exceeds 15 per cent, while the fat loss may reach 67 per cent I should not agree with Brugsch when he says that the loss of nitrogen is of subordinate importance to the fat loss, but should consider the two as of nearly equal value

FUNCTIONAL TESTS FOR THE PRESENCE OF PANCREATIC SECRETION IN THE INTESTINE

It is not my intention to consider all of the numerous tests which have been recommended, but merely to discuss two of them with which I have had experience, the Sahli glutoid capsule and the Schmidt nucleus method

Sahli's[29] glutoid capsule test depends on the fact that gelatin capsules, if hardened to the right degree in formaldehyd solution, will resist the action of the gastric juice, but will be digested by trypsin The capsules are filled with salol and swallowed by the patient, digestion of the capsule is shown by the appearance in the urine of salicyluric acid, which can be recognized by the ferric chlorid test A control test always should be made on a normal person If no reaction is found within twenty-four hours, the pancreatic secretion is considered deficient This test has been

29 Sahli, H Weitere Mittheilungen uber die diagnostische und therapeutische Verwendung von Glutoidkapseln, Deutsch Arch f klin Med, 1898, lxi, 445

criticized a good deal on account of the possibility of variations in the amount of hardening of the capsules, so that it might happen, on the one hand, that they were digested by the gastric juice in the absence of pancreatic secretion, or, on the other hand, that they remained undigested, although pancreatic secretion was present All are agreed that the test is of value only in cases of complete absence of the pancreatic juice In the three cases in my series in which it was tried (Cases 1, 2 and 4), the capsules were not digested While admitting the possibilities for error, I should assign to the test some slight value as confirmatory of the absence of pancreatic secretion, if other signs of pancreatic disease are present

The Schmidt[30] nucleus test is based on the observation of Schmidt that nuclei were digested only by trypsin, being unaffected by the other proteolytic ferments Small cubes of raw beef are hardened in alcohol, tied up in gauze sacks, washed in water and given to the patient They are recovered from the stools and sections are made and stained to see if the nuclei have been digested The time of passage should not be less than twelve or greater than thirty hours, otherwise the test must be repeated The result is called positive if all the nuclei, except those on the edge of the specimen, are preserved and take the nuclear stain According to Schmidt, a positive result under all circumstances indicates absence of the pancreatic secretion, while a negative result is not conclusive either way On theoretical grounds it has been objected that the nuclei may be digested by the gastric juice, but this objection has little weight because Schmidt attaches importance only to positive results, i e, where the nuclei remain undigested

In my hands the test has not proved of great value, and my experience is in accord with that of Brugsch,[31] Klieneberger,[32] and the late Dutton Steele[33] in this country It was positive, to be sure, in all of the present series and in one additional case of cancer of the head of the pancreas (verified by operation), but it was also positive on two occasions in a case of stone in the common duct, in which at autopsy the pancreatic ducts were patent and the gland perfectly normal, both in the gross and in the microscopical appearances And Brugsch[31] found a positive result in a case of gastric achylia in which trypsin could be demonstrated in the stools by other methods Moreover, it is not uncommon in persons with normal pancreatic function to find the nuclei well stained in the

30 Schmidt, A Ein neues diagnostisches Merkmal bei Pankreaserkrankungen Verhandl d Cong f inn Med, 1904, xxi, 335

31 Brugsch, T Zur funktionellen Darmdiagnostik Deutsch med Wchnschr, 1909, xxxv, 2307

32 Klieneberger, C Diagnostik der Pankreaserkrankungen Med Klinik, 1910, vi, 91

33 Steele, J D The Nucleus Test in Pancreatic Disease, Univ Penn Med Bull 1906-7, xix, 235

center, and unstained only in the outer quarter or so of the specimen, so that it becomes difficult to interpret the results For, according to Schmidt, bacterial action may be sufficient to digest the outermost nuclei In all my cases of pancreatic achylia, however, the nuclei were well stained everywhere except in a narrow space at the very rim of the section, so that it is probably safe to call cases with more digestion than this negative To sum up, a positive result appears to be in favor of pancreatic disease, but is encountered occasionally in other conditions, while a negative result is against total absence of the pancreatic juice, especially if free hydrochloric acid is absent in the stomach The test is of little value in partial occlusion of the pancreatic ducts, and in total occlusion it is usually superfluous, as the diagnosis may be made by other methods

SUMMARY AND CONCLUSIONS

1 The diagnosis of complete absence of pancreatic juice from the intestine can be made usually without the use of absorption experiments or complicated tests by attention to the following appearances of the feces increased bulk, the presence of fat visible to the naked eye, of microscopic fat droplets in large numbers, and of creatorrhea

2 The complete absence of pancreatic juice interferes greatly with the absorption of fat and of nitrogen

3 The fat-splitting in this condition is usually normal, sometimes decreased

4 The saponification is almost always much diminished, and the fatty acids always exceed the soaps

5 Exclusion of both the bile and pancreatic juice causes a considerably greater loss of fat, and a somewhat larger nitrogen loss than where the pancreatic juice alone is excluded

6 In the absence of icterus, a fat loss of 40 per cent or over, and a nitrogen loss of over 30 per cent point almost with certainty to pancreatic disease, provided that the following conditions are excluded diarrheal diseases, amyloid and tuberculosis of the intestine, tuberculosis of the peritoneum and mesenteric lymph-nodes If icterus is present, a fat loss of more than 50 per cent favors pancreatic disease, and the greater the loss, the stronger the probability The value of the nitrogen determination is but slightly impaired by the presence of jaundice, for in simple icterus the nitrogen loss is but slightly above the normal

7 The amount of the fat-splitting has usually but little diagnostic importance, a very great reduction, however is suggestive of pancreatic disease

8 An excess of soaps over fatty acids renders the diagnosis of complete absence of the pancreatic juice extremely improbable

9. By the administration of raw pancreas or of pancreatic preparations in pancreatic disease the absorption of fat and nitrogen as a rule can be greatly improved

10 In a case in which both the gastric and the pancreatic secretions were deficient, the absorption of nitrogen was considerably increased by the administration of hydrochloric acid and pepsin, though not to the same extent as by pancreatic preparations

I wish to express my thanks to the members of the staff of the Massachusetts General Hospital for their courtesy in placing the clinical material at my disposal, and to Professor Folin and Dr William F Boos for valuable advice in the course of the laboratory work

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THE VALUE OF ABSORPTION METHODS IN THE WASSERMANN TEST *

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It is conceded by most observers that in working with a hemolytic system it is advisable to use known amounts of both amboceptor and cells Wassermann's original method for the diagnosis of syphilis makes use of 1 c c of a 5 per cent suspension of sheep corpuscles with just twice the amount of amboceptor necessary to hemolyze these cells Since the discovery of the existence of an antisheep amboceptor in some human serums it has been a question whether this additional amount of amboceptor might not be sufficient to produce hemolysis in conjunction with a small residue of complement not fixed in the first stage of the reaction If this should occur negative results would thus be obtained in syphilitic cases

The recognition of this possibility has given rise to several modifications of the Wassermann reaction The best-known of these is probably that of Noguchi He maintained[1] that "Wassermann's original method is subject to an error arising from the presence in human serum of a varying amount of natural amboceptor capable of being reactivated by guinea-pig's complement" He found experimentally that four units of antisheep amboceptor prevent entirely the detection of one unit of syphilitic antibody The modification of the Wassermann technic devised by him has, among other advantages, that of avoiding this danger by the use of a hemolytic system consisting of human blood cells and the serum of a rabbit immunized against them

Several other methods of obviating this source of error have been suggested which still make use of sheep corpuscles as in the original Wassermann method That of Bauer,[2] in which each serum is tested for antisheep amboceptor and artificial immune serum added only to those which show an insufficient amount of natural antisheep amboceptor to give complete hemolysis with the amounts of sheep cells and complement used in the Wassermann reaction, will of course be efficient in those cases in which the human serum contains just enough amboceptor to give complete hemolysis As, however, some serums contain many times this amount of natural amboceptor, with these the source of error still remains

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1 Noguchi Jour Exper Med 1909 xi, 392

2 Bauer Sem med, 1908 xxviii 429

Jacobaeus[3] proposed absorbing the sheep amboceptor from human serum by incubating the serum, after the addition of sheep cells at 37 C for one-half hour, then centrifuging off the cells and proceeding with the Wassermann reaction according to the regular technic In a series of 257 cases he obtained about 10 per cent more positives by this method than without absorption He asserts that complementoid is also removed by this method, thus giving it the advantage of a modification introduced by Wechselmann[4] in which complementoid is removed by digesting the inactivated human serum with barium sulphate Bauer[5] had previously tried the same procedure which Jacobaeus employed, but discarded it on account of its making the serum antihemolytic He declared that this property was much increased by the addition of liver extract, thus causing negative serums to give positive reactions

S Mintz,[6] using this method in a series of thirty-eight cases, obtained thirty positive reactions against twenty-five without absorption The serums which reacted positively were all syphilitic

I have tried this method of amboceptor absorption on 305 serums regardless of the amount of natural antisheep amboceptor present The results of the Wassermann reaction on each of these serums has been compared with the result of the reaction on the same serum with the natural antisheep amboceptor present

Only fifty-three of the 305 serums contained one or more units of natural antisheep amboceptor in 0 2 c c, that is, sufficient to hemolyze completely 1 c c of a 5 per cent suspension of sheep corpuscles in the presence of one unit of complement In seventy serums there was no trace of antisheep amboceptor in 0 2 c c In the remaining 182, antisheep amboceptor was present, but in a quantity not sufficient to produce complete hemolysis

The technic employed to remove the antisheep amboceptor from the human serum was as follows To 0 5 c c of the patient's serum, after inactivation, was added 2 c c of 0 85 per cent salt solution and 0 1 c c of sheep cells After shaking, the mixture was incubated at 37 C for twenty minutes The cells were then centrifuged off and the supernatant fluid used in the Wassermann reaction, 0 5 c c of the diluted serum being used in the tube with antigen and 1 c c in the control tube without antigen, the amount of antigen, complement, etc, being correspondingly reduced to one-half the usual quantity. The remainder of the fluid was used to test the completeness of the amboceptor absorption In about

3 Jacobaeus Ztschr f Immunitatsforschung, Orig, 1911, viii, 615
4 Wechselmann Ztschr f Immunitatsforschung, 1909, iii, 524
5 Bauer Berl klin Wchnschr, 1908, xlv, 834
6 S Mintz Ztschr f Immunitatsforschung, 1911, ix, 29

one-quarter of the cases a sufficient amount of the patient's serum was used to test for remaining antisheep amboceptor in a full cubic centimeter

In all but three of the 305 serums, removal of the sheep amboceptor was complete In each of these 0 2 c c showed a faint trace of hemolytic power for sheep cells still present One additional serum showed very slight hemolytic power remaining in a full cubic centimeter but none was demonstrated in 0 2 c c

So far as the removal of antisheep amboceptor from human serum is concerned, we may conclude that the method is practically always efficient The objection to the method is that inhibitory bodies are in some way produced by this process ("Sachs-Friedberger phenomenon") which considerably slow hemolysis, there sometimes being a trace of inhibition at the end of an hour in the control tubes and in negative serums The difference in reaction between positive and negative serums is, however, clear-cut, the inhibitory action not being sufficiently marked to render the method impracticable as a means of avoiding any error which may be due to the presence of natural antisheep amboceptor

Rossi[7] asserts that incubation at 0 C for twenty minutes is as efficient in absorbing the amboceptor as incubation at 37 C, while by this method the inhibitory phenomenon does not appear ; His method is to add 0 5 c c of sheep red blood corpuscles to 1 5 c c of the patient's serum, both having been previously cooled to 0 C This mixture is kept at this temperature for from twenty to thirty minutes, then rapidly centrifuged, and the serum drawn off with a pipette In a series of sixty syphilitic cases Rossi obtained fifty positives by the Wassermann reaction and fifty-six positives after absorption

This method of absorption, as well as that at 37 C, was tried on 195 of the above 305 serums In a portion of these the Rossi technic was followed in detail With the remainder the technic was the same except that serum and cells were mixed in the proportions used for absorption at 37 C This method was found equally efficient in absorbing the antisheep amboceptor So far, however, as the avoidance of inhibitory action is concerned, it was unsuccessful, there being little if any difference in this regard between the two methods

The results of the Wassermann reactions on the 305 serums with natural antisheep amboceptor still present and on the same serums after the amboceptor had been completely removed is shown in Table 1 The results of the Wassermann reaction following absorption at 0 C did not differ in any particular from those following absorption at 37 C

7 Rossi Ztschr f Immunitatsforschung 1911, x, 321

TABLE 1.—WASSERMANN REACTION ON 305 SERUMS BEFORE AND AFTER REMOVAL OF NATURAL ANTISHEEP AMBOCEPTOR

Wassermann Reaction	Positive	Doubtful Positive	Doubtful Negative	Negative
On serums with natural antisheep amboceptor	103	16	2	184
On serums after removal of antisheep amboceptor	104	18	1	182

Those cases are classed as positive which give complete inhibition in the tube containing 0.2 c.c. of patient's serum and antigen, with complete hemolysis in the control tube containing 0.4 c.c. of patient's serum without antigen. Those in which there was a slight trace of hemolysis in the tube with antigen and complete hemolysis in the control, and those which, with complete inhibition in the tube with antigen, showed a trace of inhibition in the control, are classed as doubtful positive. Those with partial hemolysis with antigen or partial inhibition in the control are classed as doubtful negative, all others as negative.

As is shown by Table 1, there was a difference in results in but three of the 305 cases. The cases in which the reaction differed were as follows:

1. *Pyorrhea Alveolaris.*—No history of syphilis obtainable. The serum contained 5 units of antisheep amboceptor. Wassermann reaction, with antisheep amboceptor present, negative, after removal of antisheep amboceptor, doubtful positive.

2. *Syphilitic Laryngitis.*—Primary lesion fourteen years ago. Treatment previous to Wassermann reaction not known. The serum contained over 3 units of antisheep amboceptor, the exact amount not being determined. Wassermann reaction with antisheep amboceptor present, doubtful negative, after removal of antisheep amboceptor, positive.

3. *Tabes Dorsalis.*—No history of syphilis. Serum contained 2 units of antisheep amboceptor. Wassermann reaction, with antisheep amboceptor present, negative, after removal of antisheep amboceptor, doubtful positive.

TABLE 2.—CLASSIFICATION OF 423 WASSERMANN REACTIONS DONE ON SERUMS WITHOUT AMBOCEPTOR ABSORPTION

	Positive	Doubtful Positive	Doubtful Negative	Negative
Syphilis—				
Primary	6	1	0	1
Secondary, untreated	20	0	0	1
Secondary, treated	7	0	1	4
Tertiary	54	11	1	10
Latent	24	9	1	26
Congenital	2	1	0	2
General paresis	1	0	0	0
Tabes	5	2	1	2
Diseases possibly of syphilitic origin—				
Aneurysm	6	2	0	0
Aortic insufficiency	9	0	0	5
Facial paralysis	1	0	0	2
Chronic inflammations of the eye	7	2	0	13
Diseases not diagnosed clinically as syphilitic	1	2	3	177

It will be noted that in none of these cases was the variation in results a difference between a frank negative and a frank positive reaction, thus differing considerably from the results reported by Jacobaeus and other observers It will be seen from Table 2, in which are classified the last 423 Wassermann reactions done on serums without amboceptor absorption, that the figures are similar to those reported by other laboratories using the Wassermann method The 305 cases on which absorption methods were tried are among this number The three cases classed under "Diseases not diagnosed clinically as syphilitic" which gave positive or doubtful positive reactions require special mention

Rheumatoid Arthritis—Wassermann was positive, no history of syphilis obtainable Patient complained of pain and swelling in her right great toe of three weeks' duration, and pain in right ankle and left arm for one week On entrance toe was swollen, somewhat red and tender There was slight tenderness over inner aspect of left tibia Temperature was normal During the five weeks in hospital, both elbows, and several phalangeal joints were involved Patient was on mixed treatment eleven days, potassium iodid being continued nineteen days longer without improvement

Gelatinous Carcinoma of Rectum—Wassermann was doubtful positive The patient denied lues and the past history was not suggestive Diagnosis was made from section of excised portion of tumor

Lymphosarcoma of Tonsil—Wassermann was doubtful positive This woman gave a history of one miscarriage, one child born dead at term, one child dead at 22 months (cause not known) She had two living children Otherwise there was nothing suggestive in the past history Diagnosis was made from section of excised portion of tumor

In reporting results of the Wassermann reaction it is unnecessary to give in detail the technic employed, the method being so well known There are, however, certain points which, it seems to us, should be mentioned In the reactions reported here the guinea-pig serum was always titrated and care taken never to use as much as 2 units, as will very frequently be done if 0 1 c c is used The antigen used in nearly all of the 305 cases was an acetone insoluble fraction of beef heart prepared as recommended by Noguchi[8] The quantity used in the reaction was 0 01 c c This antigen was not hemolytic or anticomplementary in four times this amount and had high antigenic properties Titrated against four positive serums, it gave with one complete inhibition in one-tenth the quantity used, with a second complete inhibition in one-thirteenth, and with the other two complete inhibition in one-twentieth the quantity used

As the results obtained by the amboceptor absorption methods vary considerably from those reported by other observers, experiments were done to test the effect of the introduction of artificial amboceptor on the

8 Noguchi Serum Diagnosis of Syphilis Ed 2 1911 Phila

Wassermann reaction done with the above antigen Three serums were selected which were frankly positive with this antigen, and Wassermann reactions were done on each of these after the addition of 5, 10, and 15 units of artificial antisheep amboceptor Reactions were also done on the same serums without the addition of artificial amboceptor and after the addition of 5, 10 and 15 units, using an amount of antigen which by titration with each serum contained 2 units of antigen for that serum Each serum contained natural antisheep amboceptor but in an amount less than 1 unit This was not removed

Serum 1 contained 2 units of syphilitic antibody Wassermann reactions were positive with both strong and weak antigens With the addition of 5, 10 and 15 units of amboceptor the reactions were doubtful or negative with both antigens, but the inhibition was greater with the stronger antigen

Serum 2 contained 18 units of syphilitic antibody Wassermann reactions were frankly positive with the strong antigen, even with the addition of 5, 10 and 15 units of amboceptor With the weak antigen the serum gave a frankly positive reaction when artificial amboceptor was not added With 5 units of amboceptor the reaction was doubtful, with 10 and 15 units, negative

Serum 3 contained more than 25 units of syphilitic antibody Wassermann reactions were frankly positive with both antigens with 15 units of antisheep amboceptor present

CONCLUSIONS

From the above cases and experiments I conclude that it is possible for antisheep amboceptor in human serum to affect the Wassermann reaction, but that when an antigen of high titer is used this is possible only with serums of very low antibody content and several units of antisheep amboceptor As these two conditions, in my experience, occur but rarely in practical work, I feel that, when a strong antigen is used, the importance of antisheep amboceptor in human serum as a cause of negative reactions in syphilitic cases is not great As a routine procedure, the absorption of amboceptor is unnecessary Its removal is, however, advisable from serums which give a negative or *doubtful reaction*, and which contain a large amount of antisheep amboceptor This is easily accomplished by digestion with sheep cells It is immaterial whether this is done at 0 C, 37 C, or at room temperature

A FURTHER REPORT ON THE PRODUCTI MENTAL CHRONIC NEPHRITIS IN BY THE ADMINISTRATION URANIUM NITRATE

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In a previous report[1] I was able to show that by t uranium nitrate to guinea-pigs it is possible to prod tion which is analogous to various stages of chronic man These changes were quite constantly produc after the administration of uranium nitrate in any three ways first, after a series of frequently repeate small doses of the drug, second, after a series of inje large doses at intervals of a considerable length of ti the injection of a single sublethal dose

The earlier experiments were performed exclusi but during the past three years a large number of ex performed on guinea-pigs, rabbits and dogs in the ho previous observations and of producing the conditio different kinds which would be better suited for sec In all of these types of animals it has been possibl which are characteristic and which are very similar case It is true that the histological picture differs co which is found in human nephritis, but the gross appe in advanced cases is that of granular atrophy, and the is that of an extreme and progressive fibrosis with ac in the tubules and glomeruli, so that one cannot describe the condition as a true chronic diffuse nephri that these results are seemingly at variance with Christian and Smith,[2] who were unable to reproduc to those which I had previously reported in guinea found that in rabbits they obtained less satisfactory r nitrate than with potassium bichromate

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[*] Manuscript submitted for publication March 15, 191

[*] From the Pathological Laboratory of Cooper Medica Stanford Jr University

[*] A portion of these experiments were performed und Rockefeller Institute for Medical Research

1 Dickson, E C A Report on the Experimental Produ nitis in Animals by the Use of Uranium Nitrate, The Arc m, 5 and 6, 375

2 Smith, R M Experimental Chronic Nephritis The

Before detailing the protocols of the cases which I wish to report, it would seem advisable to describe briefly the characteristic histological picture of the lesions since they occur so constantly not only in the kidneys of the different animals of the same kind and of the same experimental series, but also in the kidneys of animals subjected to different experimental procedures and, indeed, even in the kidneys of the different kinds of animals

The kidneys all show proliferation of the interstitial connective tissue which is constantly much more marked and much more fibrous in the inner zone of the cortex From this inner fibrotic area rays of more cellular connective tissue radiate out toward the surface, and in the more severe cases which have granular surfaces these rays extend to the surface and correspond to the small depressions on it In the majority of cases the processes are fairly well restricted to the medullary rays but in the more severe cases, especially in the kidneys of dogs there is a marked diffuse proliferation of connective tissue all through the cortex so that practically no normal appearing tissue remains In all cases the connective tissue is quite cellular in the outer zone of the cortex, and in many cases there are large areas of dense round cell infiltration in the region of the larger vessels and around some of the glomeruli In many cases there is a more or less well marked proliferation of connective tissue in the outer portion of the medulla

The glomerular changes vary considerably, depending on the situation of the glomeruli in the cortex and the severity of the fibrosis of the kidney, and they are always much more severe in the inner zone of the cortex where the connective tissue proliferation is most marked In every case the glomerular lesions would seem to be of secondary nature, since in the acute uranium nephritis the glomeruli show practically no lesions [3] The most constant change is that of pyknosis and fragmentation of the nuclei in the tuft In some more severe cases there seems to be an increase in the connective tissue elements in the tufts, and in a few cases, especially in rabbits, there is distinct thickening of the capillary walls in the tufts, and a deposit of some hyaline substance in some of the tufts In the areas where there is marked fibrosis many of the glomeruli are completely collapsed In practically all cases there is more or less marked thickening of the glomerular capsules and in many there is proliferation of the capsular epithelium In many cases there is exudation into the capsular spaces, and in some there is also detached epithelium which seems to be crowded into them from the adjoining tubule In many cases the capsules are distended and form quite large cysts In those more

3 Christian has described the occurrence of small, oval or round hyaline bodies in the glomerular tufts of rabbits which were subjected to acute uranium poisoning Boston Med and Surg Jour 1908 clix 8, and THE ARCHIVES INT MED, 1911, viii, 469

severe cases in which the majority of the glomeruli are extensively damaged, the few more normal appearing glomeruli are much larger than normal, often showing over twice the normal diameter, a condition undoubtedly due to a compensating hypertrophy

There is very constantly a marked parenchymatous change in the tubular epithelium, although the extent of this depends largely on the time which has elapsed since the last injection of uranium The convoluted tubules are as a rule, less severely damaged than are the smaller tubules, but there is usually marked hydropic degeneration of the epithelium and often a coarse, granular degeneration in which the granules take a deep eosin stain Occasionally the convoluted tubules show pyknosis and desquamation of the epithelium and contain much exudate and débris in their dilated lumens A few tubules are widely dilated and form small cysts The most severe and most constant parenchymatous degeneration is found in the ascending limbs of Henle, and in the smaller connecting tubules Here there is marked pyknosis, desquamation, and often complete necrosis of the epithelium, and frequently almost complete blocking with desquamated cells and dense hyaline casts In the few cases where fatty degeneration is present it is almost wholly confined to the epithelium of the ascending limbs of Henle In the areas of fibrosis many of the tubules are collapsed and shrunken and in many places are represented by small accumulations of pyknotic and fragmented nuclei

In the majority of cases the collecting tubules are quite normal in appearance excepting for the presence of exudate desquamated cells and casts in their lumens, but in a few cases there is actual destruction and desquamation of the collecting tubule epithelium, and in some places there seems to be an attempt at regeneration of the epithelial covering

In none of the cases is there any constant and characteristic change in the smaller blood-vessels In practically all of the more fibrotic kidneys there is a definite peri-arterial fibrosis which seems to be more marked in dogs than in the other animals, but nowhere could be found changes in the intima and media of the smaller arteries such as are constantly present in chronic diffuse nephritis in man

A fairly complete review of the literature on experimental chronic nephritis may be found in my previous report,[1] and also in reports made by Ophuls,[4] Lyon,[5] Pearce[6] and Christian[7] so that a further review will not be made at this time

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4 Ophuls Experimental Chronic Nephritis Jour Am Med Assn, 1907 xlviii, 483

5 Lyon Experimental Study on the Action of Some Poisons and Toxins on the Kidney Jour Path and Bact, 1903 04, ix, 400

6 Pearce Problems of experimental nephritis THE ARCHIVES INT MED, 1910, v, 133

7 Christian Experimental Nephritis Boston Med and Surg Jour, 1908, clviii 416

The method of experiment was the same as employed in my first series The uranium nitrate was injected subcutaneously in an aqueous solution, and the number and frequency of the injections was controlled chiefly by the variations in the weight of the animals Routine urine examinations were not made except in isolated cases, but from time to time specimens of urine from the dogs were collected and subjected to the usual clinical methods of examination

The histological picture of acute uranium nephritis has been so frequently described that I shall not include in the present series any of the animals which succumbed during the first four or five weeks of the experiment

A FREQUENTLY REPEATED INJECTIONS OF SMALL DOSES

I EXPERIMENTS ON GUINEA-PIGS

Protocol 1—Guinea pig 2, 1909, received twenty six injections of 0 5 mg, and seven injections of 1 mg of uranium nitrate during 217 days The animal died after receiving the series of 1 mg doses Weight at beginning of experiment 750 gm and at the time of death 650 gm

Autopsy No subcutaneous edema, no ascites, 5 c c of urine showed much albumin and sugar and a few granular casts, kidneys normal in size, pale, capsule slightly adherent, cut surface cloudy and pale, medulla darker than cortex, liver somewhat congested, right ventricle dilated, aorta apparently normal

Microscopical Examination The connective tissue proliferation is not very marked and is confined to the inner zone of the cortex There are many areas of round cell infiltration in the cortex There is very marked parenchymatous change, especially in the smaller tubules, with much pyknosis and desquamation, and many hyaline casts

Protocol 2—Guinea pig 3, 1909 received eighty injections of 0 5 mg, and four injections of 1 mg of uranium nitrate during 696 days The animal died two days after the last injection of 1 mg Weight at beginning of experiment 550 gm, maximum weight 860 gm, weight at time of death 510 gm

Autopsy No subcutaneous edema, ascites or hydrothorax, 5 c c of urine showed *no albumin or casts, kidneys normal size, red, smooth* except for a few small dimples which are more numerous on the right kidney, capsule not adherent, cut surface cloudy, markings fairly distinct liver congested, right ventricle dilated, aorta apparently normal

Microscopical Examination Moderate proliferation in the interstitial connective tissue, in the usual location, very little parenchymatous change, glomerular and tubular changes characteristic

Protocol 3—Guinea pig 4, 1909, received seventy injections of 0 5 mg of uranium nitrate during 590 days and died on the 595th day Weight at beginning of experiment 440 gm maximum weight 790 gm, weight at time of death 720 gm

Autopsy No subcutaneous edema or urine, about 30 c c of slightly blood stained fluid removed from peritoneal sac, kidneys small, surface pale with small hemorrhagic spots, capsule not adherent, cut surface somewhat cloudy, intestines much congested, liver pale, heart and aorta apparently normal

Microscopical Examination Moderate increase of interstitial connective tissue, almost entirely located in inner zone Characteristic glomerular and tubular changes in the fibrotic areas Little parenchymatous change in tubular epithelium Many hyaline casts

Protocol 4—Guinea pig 5, 1909 received eighty six injections of 0 5 mg of uranium nitrate during 695 days, and died six days after the last injection,

weight at the beginning of the experiment 520 gm maximum weight 800 gm, weight at time of death 500 gm

Autopsy No subcutaneous edema slight ascites and hydrothorax (10 c c of fluid collected from peritoneal sac and about 1 c c from each pleural sac) A few c c of urine showed a trace of albumin but no casts kidneys about normal size dark red, capsule definitely adherent surface everywhere finely granular, cut surface bulges and is cloudy, no cysts seen lungs and liver congested right ventricle dilated aorta apparently normal

Microscopical Examination Very marked proliferation of interstitial connective tissue in both inner and outer zones of cortex many rays extend to the surface, glomeruli show characteristic changes some are cystic tubular epithelium shows little degeneration except in fibrotic areas many hyaline casts

Protocol 5—Guinea pig 6 1909 received forty-seven injections of 0 5 mg of uranium nitrate during 360 days and died on the 434th day Weight at beginning of experiment 660 gm maximum weight 770 gm weight at time of death 640 gm

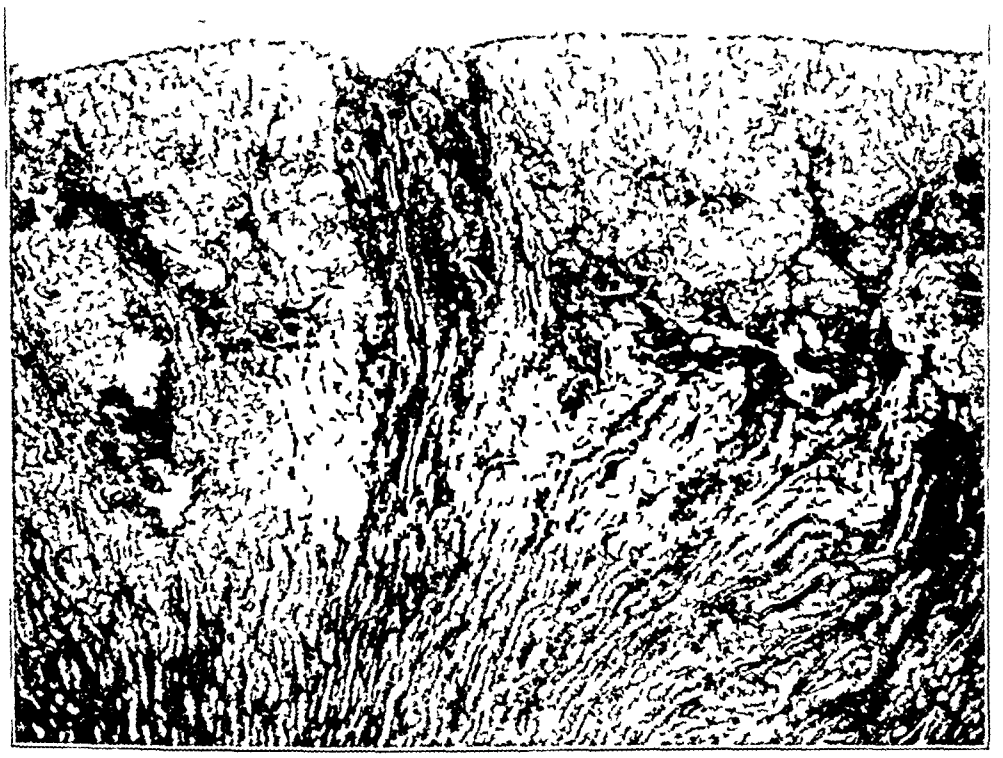

Fig 1—Guinea Pig 14 Series B, Protocol 7 × 25 Note the wide distribution of the connective tissue proliferation in the inner zone of the cortex, and the rays extending toward the surface, also the depression at the place where one ray reaches the surface

Autopsy No subcutaneous edema and no urine, there was a small amount of fluid in the peritoneal sac and the stomach was distended with fluid, kidneys slightly smaller than normal, mottled, slightly dimpled, capsule not adherent, cut surface cloudy, not swollen, liver congested heart and aorta apparently normal

Microscopical Examination Slight connective tissue proliferation in inner zone of cortex, some glomeruli show characteristic changes and a few are cystic, very marked parenchymatous change with much desquamation, many hyaline casts

Protocol 6—Guinea-pig 27, 1909, received thirty seven injections of 0 5 mg of uranium nitrate during 360 days, and died on the 429th day Weight at beginning of experiment 570 gm maximum weight 880 gm, weight at time of death 630 gm

Autopsy No subcutaneous edema and no urine, a small amount of fluid in peritoneal sac, kidneys normal size, capsule slightly adherent, surface dark red and finely granular, cut surface not cloudy, markings fairly distinct, liver and lungs congested, aorta apparently normal, right ventricle somewhat dilated

Microscopical Examination Moderate proliferation of interstitial connective tissue with many rays extending to the surface, glomeruli show usual changes, and some are cystic, there is moderate parenchymatous change with desquamation in the smaller tubules, and many hyaline casts the tubules in the fibrotic areas are shrunken and collapsed

Fig 2.—Guinea Pig 14 × 90 Note the proximity to a large blood vessel, the marked fibrosis, and the shrinkage of tubules in the fibrotic area

II EXPERIMENTS ON RABBITS

Protocol 1.—Rabbit 11, 1909, received thirty two injections of 1 mg of uranium nitrate during 196 days, and died on the 203d day Weight at beginning of experiment 3,075 gm and at the time of death 2,020 gm

Autopsy No subcutaneous edema, no ascites, and no urine Double fibrino purulent pleurisy Kidneys somewhat enlarged, surface smooth capsule not adherent, cut surface bulged and distinctly cloudy Liver congested right ventricle dilated aorta apparently normal

Microscopical Examination Marked diffuse proliferation of interstitial connective tissue, with many rays extending to the surface, and with many areas of round cell infiltration, glomeruli show thickening of capillary walls, and much

exudate in capsular spaces marked parenchymatous degeneration of tubular epithelium with much desquamation in Henle's loops and collecting tubules, and many hyaline casts marked atrophy and collapse of tubules in the fibrotic areas

Protocol 2—Rabbit 14 1909, received thirty subcutaneous injections of 1 mg of uranium nitrate during 193 days and died on the 196th day Weight at beginning of experiment 3 250 gm at time of death 2,430 gm

Autopsy No subcutaneous edema no ascites no urine, kidneys large, pale smooth, with numerous small scars on surface capsule not adherent on section was some bulging and marked opacity the cortex was pale and the medulla dark red liver congested right ventricle dilated aorta apparently normal marked double fibrino purulent pleurisy

Fig 3—Guinea-Pig 8, Series B, Protocol 1 × 100 Note the marked periarterial fibrosis, and the proximity of the damaged glomeruli to the vessel

Microscopical Examination Very marked, diffuse proliferation of interstitial connective tissue, with many large areas of round cell infiltration The majority of the glomeruli and tubules are damaged, marked parenchymatous degeneration, much desquamation in smaller tubules and many hyaline casts

Protocol 3—Rabbit 15, 1909, received thirty-three subcutaneous injections of 1 mg of uranium nitrate during 274 days, and was killed on the 457th day Weight at the beginning of the experiment 2,850 gm, at the time of death 2,950 gm

Autopsy No subcutaneous edema, slight ascites, no urine, kidneys rather small, pale and slightly granular, capsule not adherent, on the surface

were a few small hemorrhagic spots and a few small cysts On section the cut surface was pale and the cortex was apparently thinner than normal

Microscopical Examination Very marked proliferation of interstitial connective tissue, with marked inner fibrosis, and many rays extending to surface, marked glomerular changes, capillary walls of tufts thickened, and many of the capsules cystic, moderate parenchymatous change, little desquamation many tubules involved in fibrotic areas, shrunken, many hyaline casts

Protocol 4—Rabbit 18, 1909, received thirty four injections of 1 mg of uranium nitrate during 278 days and died about thirteen months after the first injection

Autopsy Kidneys rather small pale, finely granular, capsule not adherent cut surface not swollen, cortex thinner than normal

Microscopical Examination Very marked and very diffuse proliferation of interstitial connective tissue, with many rays of cellular connective tissue extending outwards from the inner fibrotic area, very many areas of round cell infiltra-

Fig 4—Rabbit 41 Series B, Protocol 12 × 40 *Note the wide distribution* of the lesion, the greater severity in the inner zone of the cortex, and the large glomerular cyst

tion in the cortex, extensive glomerular changes, thickening of capillary walls, increase in connective tissue in tufts and dilatation of capsular spaces, marked parenchymatous degeneration of tubules with much shrinkage and desquamation, marked desquamation of epithelium of collecting tubules, many hyaline casts marked atrophy and collapse of tubules in the fibrotic areas

B OCCASIONAL SUBLETHAL DOSES

1 EXPERIMENTS ON GUINEA-PIGS

Protocol 1—Guinea-pig 8 1909 received ten injections of 5 mg of uranium nitrate during 461 days and died two days after the last injection, weight at beginning of experiment 620 gm maximum weight 690 gm, weight at time of death 600 gm

Autopsy Very marked subcutaneous edema over belly and legs, no ascites, hydrothorax or urine kidneys very small about two thirds normal size, surface pale granular, capsule adherent, cut surface pale and cloudy, cortex thin, no cysts seen liver and lungs congested heart large right ventricle dilated, aorta apparently normal

Microscopical Examination Marked proliferation of interstitial connective tissue with many rays extending to the surface little round cell infiltration moderate characteristic changes in the glomeruli and tubules in the fibrotic areas some glomerular cysts, relatively little parenchymatous change in the more normal appearing tubules many hyaline casts

Protocol 2—Guinea-pig 9 1909 received six injections of 5 mg of uranium nitrate during 110 days and died seven days after the last injection, weight at beginning of experiment 725 gm at time of death 435 gm

Autopsy No subcutaneous edema no ascites no urine kidneys slightly swollen pale slightly dimpled capsule not adherent cut surface cloudy and

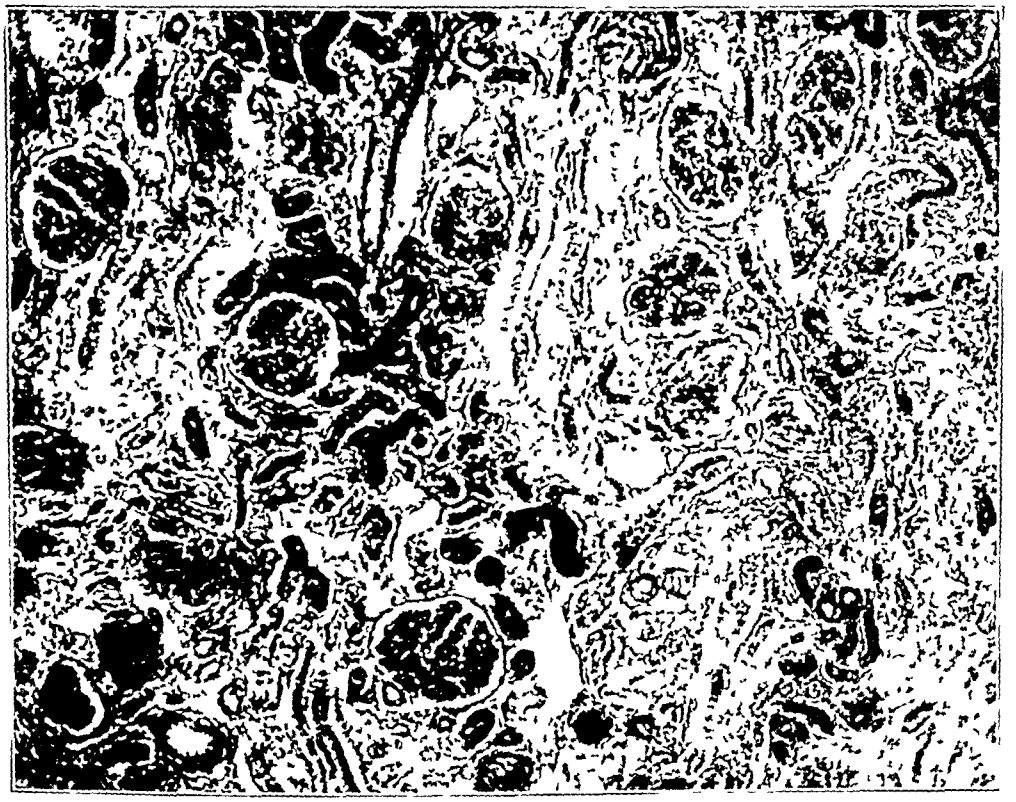

Fig 5—Rabbit 41 × 100 Note the diffuse distribution of the connective tissue proliferation, the collapse of the tubules and the pyknosis and desquamation of the tubular epithelium

swollen, cortex paler than medulla, liver congested, right ventricle dilated, aorta apparently normal

Microscopical Examination Very marked diffuse proliferation of interstitial connective tissue which is very cellular, little shrinkage, marked glomerular changes with many cysts marked parenchymatous change with much desquamation and many dense hyaline casts

Protocol 3—Guinea-pig 10, 1909, received eight injections of 5 mg of uranium nitrate during 400 days, and died five days after the last injection, weight at beginning of experiment 520 gm, maximum weight 830 gm, weight at time of death 470 gm

Autopsy Moderate subcutaneous edema over belly, thorax and legs, 30 c c fluid removed from peritoneal sac, and several c c from both pleural sacs, peri

cardium was distended with fluid to about twice normal size, no urine, kidneys about normal size, dark red, slightly dimpled, capsule slightly adherent, cut surface cloudy, not swollen, no cysts seen, liver congested, right ventricle dilated, aorta apparently normal

Microscopical Examination Slight diffuse proliferation of interstitial connective tissue and many areas of round cell infiltration, relatively little glomerular change although a few capsules are cystic, very marked parenchymatous degeneration in all tubules, much desquamation and many hyaline casts

Protocol 4.—Guinea-pig 11, 1909, received four injections of 5 mg of uranium nitrate during 248 days, and died eleven days after the last injection, weight

Fig 6.—Rabbit 50, Series B, Protocol 6 × 90 Note the dense fibrosis, the fibrous thickening of the glomerular capsules and the marked destruction of tubules in the fibrous area

at beginning of experiment 590 gm., at time of last injection 730 gm., and at time of death 855 gm., an increase of 125 gm during the last eleven days of life

Autopsy Very extreme subcutaneous edema over belly thorax and legs, very marked ascites (110 c.c. collected and at least 30 c.c. escaped), a few drops of fluid in both pleural sacs, and moderate distention of pericardium, no urine, kidneys swollen, surface mottled, smooth capsule not adherent, cut surface bulging edematous and cloudy liver congested and containing small focal necroses, moderate perihepatitis and perisplenitis spleen large, right ventricle markedly dilated aorta apparently normal

Microscopical Examination Some cellular proliferation of interstitial connective tissue and a few areas of round cell infiltration, relatively little glomerular change, very marked parenchymatous change, much desquamation and a few hyaline casts

Protocol 5—Guinea-pig 12 1909 received four injections of 5 gm of uranium nitrate during seventy-five days and died nine days after the last injection, weight at beginning of experiment 410 gm., maximum weight 480 gm., weight at time of death 295 gm

Autopsy No subcutaneous edema no ascites no urine, kidneys normal size, surface smooth with small dimples and a few pin point hemorrhages capsule not

Fig 7—Rabbit 106, Series B, Protocol 11 × 90 Note the marked increase in fibrous tissue, the dense round cell infiltration the thickening of the glomerular capsules, and the atrophy of the tubules

adherent, cut surface swollen and cloudy, liver congested, right ventricle dilated, aorta apparently normal

Microscopical Examination Slight cellular proliferation of connective tissue in inner zone of cortex and a few areas of round cell infiltration around some of the glomeruli, very marked parenchymatous change affecting all tubules, very numerous hyaline casts and a few cystic glomeruli

Protocol 6—Guinea-pig 13, 1909, received four injections of 5 mg of uranium nitrate during seventy seven days, and died three days after the last injection, weight at beginning of experiment 540 gm., weight at time of death 500 gm

Autopsy No subcutaneous edema, no ascites, no urine, kidneys normal size, surface shows few small dimples, capsule not adherent, cut section cloudy a few small cysts, liver congested, right ventricle dilated, aorta apparently normal

Microscopical Examination Slight cellular infiltration in inner zone of cortex with some areas of round cell infiltration in outer zone, little glomerular and tubular change, a few glomerular cysts and a few hyaline casts

Protocol 7.—Guinea pig 14, 1909, received seven injections of 5 mg of uranium nitrate during 400 days, and died seven days after the last injection, weight at beginning of experiment 550 gm maximum weight 680 gm, weight at time of death 310 gm

Autopsy No subcutaneous edema or hydrothorax, a few c c of ascitic fluid removed from peritoneal sac, 5 c c of urine showed a trace of albumin but no casts, kidneys small pale fibrous in appearance, surface granular, capsule adherent cortex thin, cut surface slightly opaque Liver and lungs congested left ventricle seems thicker than normal aorta apparently normal

Microscopical Examination Very marked diffuse proliferation of interstitial connective tissue and many large areas of round cell infiltration, very marked glomerular and tubular destruction in the fibrotic areas, little parenchymatous change in the more normal appearing tubules, many dense hyaline casts

Fig 8.—Dog 6 Series 1909 Protocol 5 Actual size Note the marked dimpling of the surface, and the tears where the capsule was adherent

Protocol 8.—Guinea-pig 17, 1909, received two injections of 10 mg of uranium nitrate, with an interval of seventy-seven days, and died seven days after the last injection, weight at beginning of experiment 570 gm, weight ten days before death 650 gm weight at time of death 380 gm

Autopsy No subcutaneous edema, no ascites, no urine, kidneys swollen, mottled, cloudy and smooth, capsule not adherent liver congested, right ventricle dilated, aorta apparently normal

Microscopical Examination Fairly diffuse cellular proliferation of interstitial connective tissue in inner zone of cortex, very marked parenchymatous degeneration with much desquamation and many hyaline casts, a few glomeruli contain exudate in their capsular spaces and some are dilated into small cysts

Protocol 9.—Guinea-pig 18 1909, received three injections, respectively, of 15 10 and 5 mg of uranium nitrate during 485 days and died eleven days after the last injection, weight at beginning of experiment 800 gm, maximum weight 910 gm weight at time of death 540 gm

Autopsy No subcutaneous edema 10 c c ascitic fluid and about 1 c c of fluid in each pleural sac and in pericardial sac kidneys small pale, granular with

adherent capsule cortex thin cut surface cloudy no cysts seen 10 c c urine showed heavy cloud of albumin but no casts

Microscopical Examination Moderate diffuse proliferation of interstitial cellular connective tissue many areas of round cell infiltration and moderate fibrosis around the larger blood vessels moderate glomerular change with many large cysts moderate parenchymatous change especially in the smaller tubules, many hyaline casts

Protocol 10—Guinea pig 19 1909 received two injections of 10 mg of uranium nitrate with an interval of seventy seven days and died five days after the second injection

Autopsy No subcutaneous edema ascites or urine kidneys mottled smooth, with a few dimples capsule not adherent cortex cloudy liver congested heart and aorta apparently normal

Microscopical Examination Practically the same as described in Protocol 8

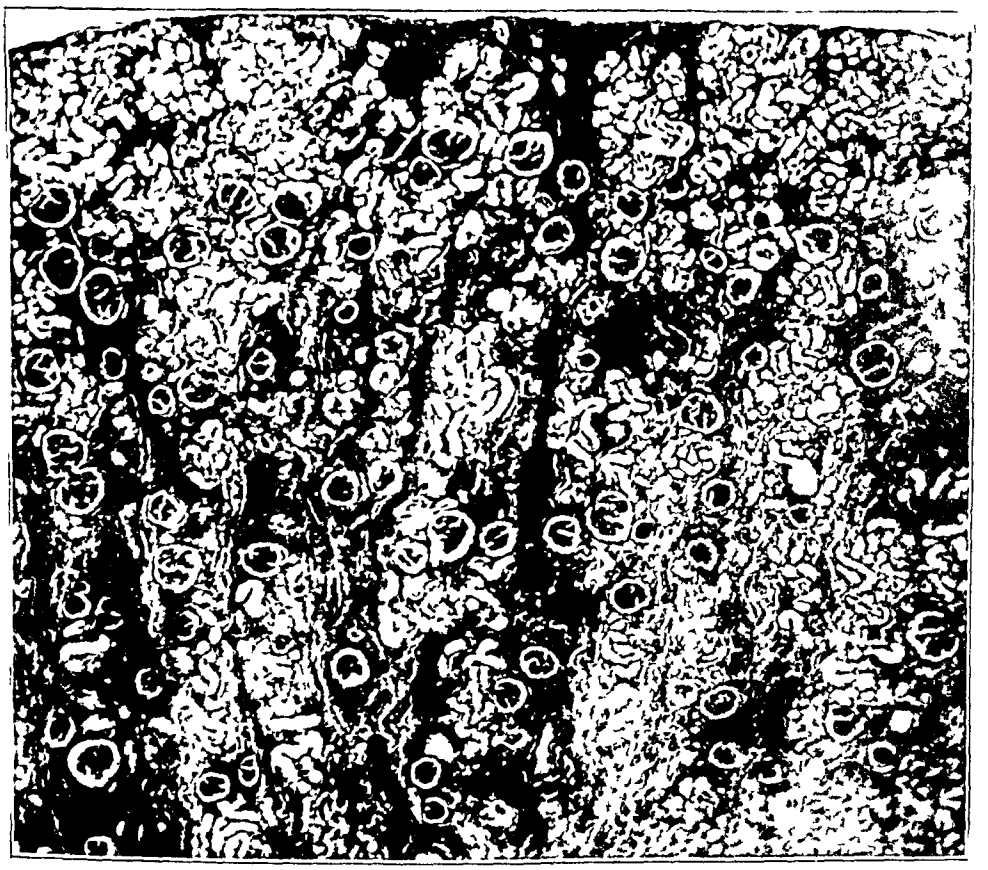

Fig 9—Dog 3, Series 1910 Protocol 8 × 25 Note the wide distribution and the severity of the lesions, the greater amount of connective tissue proliferation in the inner zone of the cortex and the radiating rays extending toward the surface

Protocol 11—Guinea pig 20, 1909, received three injections, respectively of 10, 5 and 5 mg of uranium nitrate during 485 days, and died five days after the last injection Weight at beginning of experiment 610 gm , maximum weight 750 gm , weight at time of death 505 gm

Autopsy Moderate subcutaneous edema, moderate ascites and a few c c of urine which showed definite albumin and many granular casts, kidneys large, swollen, congested, capsule not adherent, cut surface swollen and cloudy, liver and lungs congested, right ventricle dilated, aorta normal

Microscopical Examination Irregularly scattered areas of fibrosis and diffuse proliferation of interstitial cellular connective tissue in cortex, marked cystic

dilatation of both tubules and glomeruli, the majority of the glomeruli show little damage relatively little parenchymatous change, many hyaline casts

B EXPERIMENTS ON RABBITS

Protocol 1—Rabbit 23, 1909 received 5 injections of 5 mg of uranium nitrate during 111 days, and died on the 175th day

Autopsy No subcutaneous edema or ascites Fifty c c of urine showed very marked albumin and many hyaline and granular casts Kidneys swollen, dark red surface smooth, capsule not adherent, cut surface cloudy Liver congested, heart and aorta apparently normal

Microscopical Examination Marked proliferation of interstitial connective tissue Marked glomerular change, with a hyaline deposit in some of the tufts Many hypertrophied glomeruli Marked destruction of tubules in fibrotic areas relatively little parenchymatous change in more normal appearing tubules Many hyaline casts

Fig 10—Dog 3, Series 1910 × 100 Note the extreme fibrosis and round cell infiltration the thickening and beginning cyst formation of the glomerular capsules, and the marked tubular destruction

Protocol 2—Rabbit 24, 1909, received four injections of 5 mg of uranium nitrate during eighty one days, and died seven days after the last injection

Autopsy No subcutaneous edema and no ascites, 10 c c of urine showed a moderate cloud of albumin and many granular casts, kidneys large, surface shows many small scars and some small hemorrhages, capsule slightly adherent cut surface cloudy and swollen liver congested, left ventricle seemed thicker than normal, aorta apparently normal

Microscopical Examination Very marked diffuse proliferation of interstitial connective tissue involving the whole cortex and outer part of the medulla little fibrosis and little shrinkage, moderate glomerular change with some fibrosis and some hyaline deposit in the tufts many of the tubules are separated by cellular proliferation of connective tissue, marked parenchymatous change some desquamation and many hyaline casts

Protocol 3—Rabbit 25 1909, received three injections of 5 mg of uranium nitrate during seventy-four days, and was killed on the 281st day, weight at beginning of experiment 2 200 gm , at the time of death 2,930 gm

Autopsy No subcutaneous edema or ascites, urine showed no albumin or casts kidneys normal size congested, capsule not adherent surface smooth with few small scars cut surface not swollen or cloudy heart, liver and aorta normal

Microscopical Examination Scattered areas of cellular connective tissue proliferation in cortex and a few small areas of fibrosis in inner zone majority of glomeruli and tubules normal a few glomeruli have thickened capsules and pyknosis and fragmentation of nuclei and a few tubules show hydropic and some granular degeneration

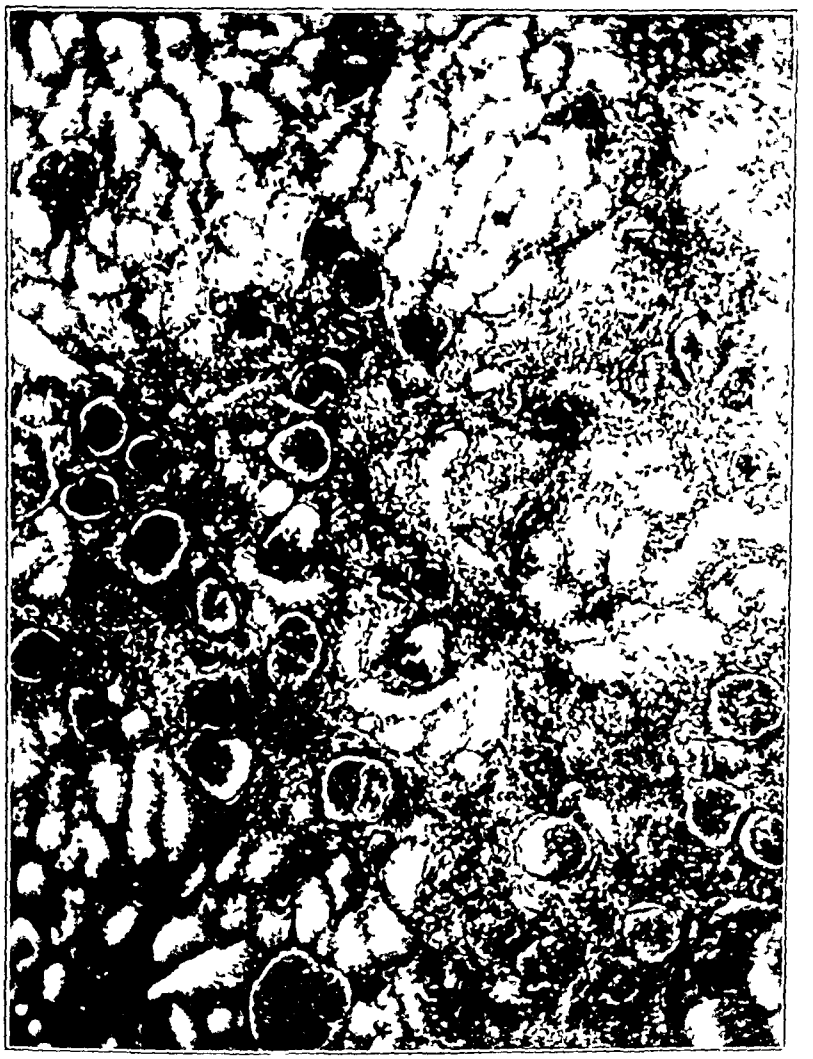

Fig 11—Dog 5, Series 1909, Protocol 4 × 90 Note the extreme degree of connective tissue proliferation, the cellular character of the newly-formed connective tissue, the marked shrinkage of the glomeruli, and the extensive tubular destruction

Protocol 4—Rabbit 26, 1909, received two injections of 5 mg of uranium nitrate, with an interval of thirty-two days, and died seven days after the second injection

Autopsy No subcutaneous edema and no ascites, 25 c c urine showed a trace of albumin and many hyaline and epithelial casts, kidneys swollen, congested surface smooth and mottled, capsule not adherent, cut section swollen and opaque liver large and congested, heart and aorta normal

Microscopical Examination Very marked diffuse, cellular proliferation of interstitial connective tissue in outer and inner zone of cortex, little fibrosis, many large areas of round cell infiltration in cortex and medulla, moderate glomerular and tubular change in fibrotic areas and marked parenchymatous degeneration with some desquamation and many hyaline casts

Protocol 5—Rabbit 27, 1909, received three injections of 5 mg of uranium nitrate during seventy four days and was killed on the 112th day There had been a large abscess on the shoulder for about three weeks previous to death

Autopsy No subcutaneous edema slight ascites and 30 c c of urine which showed a trace of albumin but no casts kidneys large, pale, smooth with a few dimples, capsule not adherent, cut surface swollen, cloudy and edematous, liver congested, heart and aorta apparently normal

Fig 12—Dog 6 Series 1909, Protocol 5 × 60 Note the very marked peri arterial fibrosis

Microscopical Examination Marked proliferation of interstitial connective tissue, with many areas of round cell infiltration in cortex, very marked glomerular and tubular change, especially in inner zone of cortex many large glomerular cysts, marked parenchymatous change in tubules, much desquamation and many hyaline casts

Protocol 6—Rabbit 50, 1910, received one injection of 5 mg, and two injections of 3 mg of uranium nitrate during 158 days, and died on the 264th day Weight at beginning of experiment 1 680 gm maximum weight 2,460 gm, weight at time of death 1 175 gm

Autopsy No subcutaneous edema a few c c of ascitic fluid, and 15 c c urine, which showed a trace of albumin, many hyaline and waxy casts, and a few granular casts, kidneys small, pale, capsule not adherent, surface finely granular, cut section opaque, cortex thin, medulla edematous, liver congested, right ventricle dilated, left ventricle distinctly thicker than normal, aorta apparently normal

Microscopical Examination Marked diffuse proliferation of interstitial connective tissue Marked glomerular change in inner zone of cortex, and some compensatory hypertrophy of glomeruli in outer zone moderate parenchymatous change, some desquamation, and a few hyaline casts

Protocol 7—Rabbit 61, 1910, received three injections of 3 mg of uranium nitrate during 150 days, and died on the 190th day Weight at beginning of experiment 1,680 gm, maximum weight 1,810 gm, weight at time of death 1 390 gm

Autopsy No subcutaneous edema and no ascites, 10 c c of urine showed a faint trace of albumin but no casts, kidneys small, pale, finely granular, capsule not adherent, cut surface opaque, lungs and liver congested, heart dilated, aorta apparently normal

Microscopical Examination Moderate diffuse proliferation of interstitial connective tissue, relatively little glomerular change, marked parenchymatous change, especially in smaller tubules, many hyaline casts

Protocol 8—Guinea-pig 63, 1910, received three injections of 3 mg, and one injection of 2 mg of uranium nitrate during 202 days, and died on the 242d day Weight at beginning of experiment 1,730 gm, maximum weight 2,210 gm, weight at time of death 1,860 gm

Autopsy No subcutaneous edema, marked adhesive peritonitis with old adhesions between all viscera, 10 c c of urine showed definite cloud of albumin but no casts, kidneys normal size, pale, mottled, finely granular, capsule not adherent, cut surface opaque, liver and lungs congested, right ventricle widely dilated, left ventricle in extreme systole, hard, and apparently definitely hypertrophied, aorta normal

Microscopical Examination Moderate diffuse proliferation of interstitial connective tissue, with many areas of round cell infiltration scattered irregularly through the cortex, moderate glomerular change, with some compensatory hypertrophy of glomeruli in the outer zone, moderate parenchymatous change, and many dense hyaline casts

Protocol 9—Rabbit 67, 1910, received three injections of 3 mg of uranium nitrate during 150 days, and died on the 175th day, weight at beginning of experiment 1,720 gm, maximum weight 2,010 gm, weight at time of death 1,250 gm

Autopsy No subcutaneous edema, ascites or hydrothorax, 20 c c urine showed a trace of albumin but no casts, kidneys small, slightly congested, surface smooth with a few dimples, capsule not adherent, cut surface cloudy, some edema in pyramids, liver and lungs congested, right ventricle dilated, aorta apparently normal

Microscopical Examination Moderate diffuse proliferation of interstitial connective tissue which is much more cellular than usual, moderate glomerular change especially in inner zone moderate parenchymatous change with desquamation, and many hyaline casts

Protocol 10—Rabbit 68, 1910, received three injections of 3 mg of uranium nitrate during 150 days, and died six days after the last injection, weight at beginning of experiment 1,580 gm, maximum weight 1,780 gm, weight at time of death 1,200 gm

Autopsy No subcutaneous edema or ascites, a few c c of urine showed a marked cloud of albumin, many hyaline and a few granular casts, kidneys about normal size, capsule not adherent, surface dark red in color and everywhere covered by many large scars, cut surface cloudy

Microscopical Examination Very marked diffuse proliferation of interstitial connective tissue, and many areas of round cell infiltration in cortex, fairly

marked glomerular changes, marked parenchymatous degeneration of tubular epithelium, many hyaline casts

Protocol 11.—Rabbit 106, 1910, received two injections of 3 mg of uranium nitrate with an interval of 105 days, and died on the 127th day. Weight at beginning of experiment 2,260 gm., at time of death 1,200 gm.

Autopsy. No subcutaneous edema or ascites, right sided pleuropneumonia. A few c.c. of urine showed a trace of albumin and some hyaline casts, kidneys small, capsule adherent, surface pale and finely granular, cut surface pale, cortex thin, liver congested, right ventricle dilated, aorta apparently normal.

Microscopical Examination. Very marked diffuse proliferation of interstitial connective tissue with many rays extending to surface, and much diffuse proliferation of connective tissue between the rays, moderate glomerular change, and marked parenchymatous degeneration of tubular epithelium with some desquamation and many hyaline casts.

Protocol 12.—Rabbit 41, 1910, received five injections of 3 mg. and one injection of 6 mg. of uranium nitrate during seventy-two and one-half weeks, and died thirty-six days after the last injection. Weight at beginning of experiment 1,660 gm., maximum weight 2 720 gm., weight at time of last injection 2,550 gm., and weight at time of death 1,770 gm.

Autopsy. No subcutaneous edema, moderate ascites, hydrothorax and hydropericardium, 20 c.c. urine showed much albumin and a few hyaline casts, kidneys large, mottled, capsule not adherent, surface finely granular, cut surface pale, cortex distinctly narrow, much edema in medulla, liver large, firm, rough with evidence of passive congestion and increase in connective tissue, heart large, left ventricle evidently hypertrophied, right ventricle dilated, lungs congested, *adrenals large, spleen and aorta apparently normal, chronic adhesive peritonitis*.

Microscopical Examination. Very marked diffuse proliferation of interstitial connective tissue with many rays extending to the surface, much proliferation in areas of cortex between the rays, and much round cell infiltration, moderate glomerular change, much pyknosis and fragmentation of nuclei of tufts, little thickening of capsule or proliferation of capsular epithelium, some exudate into capsular spaces and moderate cyst formation, very marked parenchymatous degeneration with complete necrosis in many tubules and much desquamation, evidence of epithelial regeneration in many tubules, few hyaline casts, marked periarterial fibrosis around many of medium sized and larger arteries.

EXPERIMENTS ON DOGS

The injections on dogs during the earlier experiments were made somewhat at random in order to ascertain the degree of tolerance of these animals for the drug, as well as the effects which would be produced on the kidneys. At times the injections were repeated at frequent, and at other times, at much longer intervals. It was found that the best results were obtained either when fairly large amounts of the drug were injected during as short a period of time as the animal could stand, or, when almost sublethal doses were given, at longer intervals. The maximum dose which can be used with safety is approximately 3 mg. per kilogram of weight. This amount produces a fairly acute attack of nephritis from which the animal usually recovers, and can often be safely repeated several times at intervals of several weeks. In every case, however, the initial dose should be somewhat smaller than this, and subsequent treatment should be based on the reaction which the animal shows to the first injection.

Protocol 1—Dog 2, 1909, a female fox terrier about 5 months old, received two injections of 5 mg and one injection of 10 mg of uranium nitrate during fifty days, and was killed thirty-three weeks after the first injection The weight at time of death was 5 kilos The urine several times showed albumin and some casts

Autopsy No edema, no ascites, urine free from albumin or casts, kidneys small, slightly mottled, capsules slightly adherent cut surface opaque but not swollen, heart, liver lungs and aorta apparently normal

Microscopical Examination Little increase in interstitial connective tissue except around the larger blood vessels, several large areas of round cell infiltration in cortex around blood vessels and glomeruli, some glomerular change in inner zone of cortex, some parenchymatous change more marked in tubules in region of round cell infiltration no casts seen

Protocol 2—Dog 3 1909, a mongrel male about 5 months old, received two injections of 5 mg and one of 10 mg of uranium nitrate during fifty days, and was killed thirty-four weeks after the first injection Albumin and a few hyaline casts were found once during the course of the experiment Weight at time of death 10 26 kilos

Autopsy No edema and no ascites urine showed many hyaline and granular casts, but no albumin kidneys about normal size, slightly mottled capsule slightly adherent, cut surface cloudy, liver, lungs and aorta apparently normal, heart large and flabby, weight 80 *gm*, and the heart to body ratio 0 00779

Microscopical Examination No diffuse proliferation of interstitial connective tissue, but many foci of cellular proliferation are scattered irregularly through the cortex, some glomerular change, especially near the areas of newly-formed connective tissue In the inner zone a few glomeruli show almost complete fibrosis of the tufts, and some are cystic, relatively little parenchymatous change, some exudate and desquamation and a few hyaline casts

Protocol 3—Dog 4, 1909, a mongrel male about 5 months old, received one injection of 10 mg, and one of 20 mg of uranium nitrate within seventeen days, and was killed thirty-one weeks after the first injection Weight at time of death 14 28 kilos The urine showed albumin and casts several times during the course of the experiment

Autopsy No edema or ascites, urine showed a few hyaline casts but no albumin kidneys slightly larger than normal, mottled, capsule not adherent, surface slightly dimpled, cut surface cloudy and edematous, pyramids more congested than the cortex, liver and lungs congested, aorta apparently normal, heart large, left ventricle apparently hypertrophied, right ventricle dilated, weight 118 gm, and heart to body ratio 0 00802

Microscopical Examination Little new formation of fibrous tissue except around the larger blood vessels, several large areas of cellular infiltration in cortex where round cells and fibroblasts widely separate the kidney tubules, little glomerular change except in the areas of cellular proliferation, very marked parenchymatous change in practically all tubules, much pyknosis and desquamation in the smaller tubules, and many dense, hyaline casts

Protocol 4—Dog 5, 1909, a mongrel male about 5 months old, received two injections of 10 mg of uranium nitrate during seventeen days, and was found dead fourteen weeks after the first injection Weight at time of death 5 kilos

Autopsy No edema, ascites or urine, kidneys small, pale with minute hemorrhages, capsule thick and firmly adherent, surface torn and rough, with numerous large and smaller depressions, no cysts seen cut surface white and fibrous, markings almost obliterated, cortex very narrow, liver large and congested, heart large, left ventricle firm and appears hypertrophied, aorta apparently normal, weight of heart not obtained

Microscopical Examination Very marked proliferation of interstitial connective tissue in both cortex and medulla, and marked fibrous thickening of the capsule, newly-formed connective tissue very fibrous in inner zone of cortex

from which more cellular rays extend to surface, marked, diffuse connective tissue proliferation in areas of cortex between the rays, practically all glomeruli extensively involved, much fibrosis of tufts and thickening of capsules, but no cyst formation A few glomeruli show compensatory hypertrophy, very extensive tubular destruction with much desquamation in smaller tubules, and extreme atrophy of tubules in the fibrotic areas, much more fibrosis in medulla than usual, no casts seen

Protocol 5—Dog 6, 1909, a mongrel male about 5 months old, received two injections of 10 mg of uranium nitrate during seventeen days, and was killed twenty-nine weeks after the first injection Albumin but no casts were found twice during life Weight at time of death 5 61 kilos

Autopsy No subcutaneous edema and no ascites, 30 c c urine showed many granular and hyaline casts but no albumin, kidneys small, pale, capsules firmly adherent, surface torn, finely granular, with some large scars and a few small cysts, cut surface very pale and fibrous, cortex thin, medulla white and glistening, liver large and congested, aorta apparently normal, heart large, left ventricle thick and firm, right ventricle dilated, weight 60 gm , heart to body ratio 0 01069

Microscopical Examination Very marked diffuse proliferation of interstitial connective tissue, more marked and more fibrous in inner zone of cortex, with more cellular rays extending to the surface, much diffuse proliferation of connective tissue in cortex between the rays, and many areas of round cell infiltration, very marked change in practically all glomeruli, much shrinkage and capsular thickening, and many small cysts, some glomeruli show compensatory hypertrophy, practically none of the tubules normal, much dilatation of lumens, little desquamation of epithelium but much exudate, much increase in fibrous tissue in medulla, very few casts seen

Protocol 6—Dog 1, 1910, a mongrel female about 9 months old, received four injections of 10 mg and three injections of 20 mg of uranium nitrate during forty-five weeks, and was accidentally killed sixty-one weeks after the first injection Weight at beginning of experiment 7 5 kilos, weight at time of death 7 68 kilos

Autopsy No subcutaneous edema or ascites, no urine, kidneys small, reddish brown in color, capsule slightly adherent, surface slightly granular, cut surface apparently normal, liver, lungs and aorta normal, heart rather large, in diastole, weight 61 5 gm , heart to body ratio 0 00800

Microscopical Examination Marked proliferation of interstitial connective tissue, quite cellular in outer zone, much round cell infiltration, moderate glomerular change, marked parenchymatous change, much fat, especially in ascending limbs of Henle, little desquamation, much shrinkage in areas of fibrosis, few hyaline casts

Protocol 7—Dog 2, 1910, a male spaniel, about 6 months old, received three injections of 5 mg, one injection of 10 mg, and two injections of 20 mg of uranium nitrate during fifty-three weeks, and was killed seventy one weeks after the first injection Weight at beginning of experiment 5 25 kilos, weight at time of death 16 3 kilos

Autopsy No subcutaneous edema, no ascites, no urine, kidneys about normal size, dark red, capsule slightly adherent, surface smooth, cut surface opaque and slightly edematous, liver, lungs, adrenals and aorta apparently normal, heart large right side dilated, weight 145 gm , heart to body ratio 0 00888

Microscopical Examination Marked diffuse proliferation of interstitial connective tissue which is quite cellular, and many large areas of round cell infiltration, marked change in many of the glomeruli, with lobulation and shrinkage of tufts and thickening of capsules, in some glomerular spaces there are masses of epithelium which are evidently pushed in from the tubules, a few glomeruli show compensatory hypertrophy, very marked parenchymatous change in all tubules, marked desquamation in smaller tubules, a few casts

Protocol 8—Dog 3, 1910, a mongrel male, about 9 months old, received two injections of 10 mg, two of 30 mg, and three of 50 mg of uranium nitrate during fifty-three weeks, and was killed sixty weeks after the first injection, weight at beginning of experiment 14 2 kilos, weight at time of death 21 6 kilos, urine examinations during life showed traces of albumin and a few hyaline casts

Autopsy No subcutaneous edema, no ascites, no urine, kidneys normal in size, brownish in color, capsule slightly adherent, surface fairly smooth, cut surface cloudy, cortex slightly narrower than normal, liver, pancreas and aorta apparently normal heart large, left ventricle firm and thick, weight 180 gm , heart to body ratio 0 00818

Microscopical Examination Very marked diffuse proliferation of interstitial connective tissue which in most places does not reach the surface, many areas of round cell infiltration, marked glomerular change, many tufts shrunken, distinct fibrosis of some tufts, much exudate in spaces and marked thickening of capsules, many glomeruli are hypertrophied, very marked parenchymatous change in all tubules, much desquamation, much fatty degeneration in convoluted tubules and ascending limbs of Henle, no casts seen

Protocol 9—Dog 5, 1910, a black and tan male about 9 months old, received three injections of 10 mg and one of 30 mg of uranium nitrate during twenty-three weeks and died eleven days after the last injection Weight at beginning of experiment 8 98 kilos, and at time of death 8 02 kilos

Autopsy No subcutaneous edema and no ascites, 30 c c of urine in bladder showed much albumin but no casts, kidneys firm, swollen, congested, capsule slightly adherent, surface smooth, cut surface swollen and cloudy, liver, lungs and aorta apparently normal, heart large, right ventricle dilated, left ventricle apparently enlarged, weight 73 gm

Microscopical Examination Moderate increase in interstitial connective tissue, many areas of round cell infiltration very little glomerular change, marked parenchymatous change with some desquamation and many hyaline casts

Protocol 10—Dog 7, 1910, a mongrel male about 8 months old, received three injections of 10 mg, two of 30 mg and three of 40 mg of uranium nitrate during fifty-three weeks, and died thirteen days after the last injection, weight at beginning of experiment 8 9 kilos, weight at time of last injection 12 9 kilos, and weight at time of death 10 5 kilos

Autopsy No subcutaneous edema, no ascites, 3 c c urine showed much albumin and a few granular casts, kidneys about normal size, very pale, capsule slightly adherent, surface distinctly granular with fine and coarser nodules, cut surface pale and very opaque, cortex thin, liver and lungs congested aorta apparently normal, heart large and flabby, many subendocardial hemorrhages, all chambers dilated

Microscopical Examination Moderate, diffuse, cellular proliferation of interstitial connective tissue with very marked periarterial fibrosis, moderate glomerular change, very extreme parenchymatous change with almost complete loss of nuclear staining, very marked desquamation, much exudate, and many hyaline casts

Protocol 11—Dog 11, 1910, a mongrel male, received two injections of 50 mg and three injections of 30 mg during forty weeks, and died eight days after the last injection, weight at beginning of experiment about 12 kilos, weight at time of death 9 9 kilos Daily routine urine examinations after each of the first three injections showed the characteristic urinary findings of acute uranium poisoning, with much albumin and sugar, and many granular casts

Autopsy No subcutaneous edema or ascites, 10 c c urine showed much albumin and sugar, and many granular and cellular casts, kidneys rather small, pale, capsule slightly adherent, surface slightly granular, cut surface cloudy, cortex narrow, liver and lungs congested, aorta apparently normal, heart dilated in all chambers, weight 76 gm

Microscopical Examination Moderate diffuse proliferation of cellular interstitial connective tissue with little fibrosis excepting around the larger vessels Moderate glomerular change, no glomerular cysts, very marked parenchymatous change, much desquamation in smaller tubules much exudate and many casts

Protocol 12—Dog 12, 1910, a young terrier female, received one injection each of 30, 50 and 40 mg of uranium nitrate during twelve weeks, and died four weeks after the last injection Weight at beginning of experiment 10 5 kilos, maximum weight 15 8 kilos, weight at time of death 12 9 kilos

Autopsy No subcutaneous edema, ascites or urine, kidneys large, dark red, capsule slightly adherent, surface slightly granular, cut surface moist and cloudy, no cysts seen, liver and lungs congested, aorta apparently normal, heart dilated, numerous subendocardial ecchymoses in left ventricle, weight 85 gm

Microscopical Examination Moderate, diffuse and very cellular proliferation of interstitial connective tissue, with many large areas of round cell infiltration, relatively little glomerular change, few glomerular cysts, marked parenchymatous change, much flattening of tubular epithelium, some desquamation and much exudate, few casts seen

Protocol 13—Dog 15, 1910, a fox terrier female about 8 months old, received one injection each of 15 mg and 20 mg of uranium nitrate with an interval of nine weeks, and died eleven days after the last injection Weight at beginning of experiment 5 3 kilos, weight at time of last injection 5 2 kilos, weight at time of death 3 6 kilos

Autopsy No subcutaneous edema and no ascites, 15 c c urine showed much albumin, moderate glycosuria, very many granular, and many waxy casts, kidneys swollen, congested, capsule not adherent, surface smooth, cut surface bulges, cortex wide and opaque, liver and lungs congested, aorta apparently normal, heart small, right ventricle dilated

Microscopical Examination Slight diffuse cellular proliferation of interstitial connective tissue, many areas of round cell infiltration, little glomerular change, some parenchymatous degeneration with little desquamation, no casts seen

Protocol 14—Dog 17, 1910 a fox terrier female about 8 months old, received two injections of 20 mg of uranium nitrate with an interval of nine weeks, and died 11 days after the last injection Weight at beginning of experiment 7 7 kilos, weight at time of death 5 kilos

Autopsy No subcutaneous edema and no ascites, 5 c c urine showed much albumin, some sugar, very many granular, and a few cellular casts, kidneys large, swollen congested, capsule not adherent, surface smooth, cut surface bulges and is opaque, liver and lungs congested, aorta apparently normal, heart large, right side dilated, weight 50 gm

Microscopical Examination Slight, diffuse, cellular proliferation of interstitial connective tissue with rays extending almost to periphery in places, glomeruli show some exudate but little chronic change, very marked parenchymatous change, almost complete necrosis of epithelium, much desquamation and many casts

Protocol 15—Dog 19, 1910, a fox terrier female about 6 months old, received six injections of 10 mg of uranium nitrate during eleven weeks, the first five being given during the first five weeks, and died five weeks after the last injection Weight at beginning of experiment 3 7 kilos, weight at time of last injection 4 7 kilos, weight at time of death 2 5 kilos

Autopsy No subcutaneous edema and no ascites, 10 c c urine showed much albumin and sugar and very many granular and hyaline casts, kidneys small, pale, firm, capsule adherent, surface roughened, cut surface pale and opaque, liver, lungs and aorta apparently normal, heart small, not dilated, weight 26 gm

Microscopical Examination Slight cellular proliferation of interstitial connective tissue in inner zone of cortex with rays extending outwards to the surface, very little glomerular change, very marked parenchymatous change with almost complete necrosis of epithelium in many tubules, few casts

Protocol 16—Dog 22, 1910, a fox terrier female about 6 months old received six injections of 5 mg of uranium nitrate during eleven weeks, and died twenty-five weeks after the first injection, weight at beginning of experiment 4 4 kilos, weight at time of last injection 5 6 kilos, weight at time of death 4 3 kilos

Autopsy No subcutaneous edema and no ascites, 15 c c urine showed much albumin, some sugar and very many hyaline and partly granular casts, kidneys small, pale, capsule slightly adherent, surface smooth, cut surface cloudy and bulging, medulla darker than cortex, liver and lungs congested, aorta apparently normal, heart small, not dilated, weight 38 gm

Microscopical Examination Very marked, fairly diffuse cellular proliferation of interstitial connective tissue which in most places does not reach to the surface, moderate glomerular change, some exudate and some cysts, very marked parenchymatous change, marked fatty degeneration especially in Henle's loops, little desquamation and no casts

Protocol 17—Dog 24, 1910, a mongrel female about 6 months old, received seven injections of 5 mg of uranium nitrate during thirty-one weeks, the first five being given during the first five weeks, and died nine days after the last injection Weight at beginning of experiment 5 6 kilos, weight at time of last injection 6 9 kilos weight at time of death 5 2 kilos

Autopsy No subcutaneous edema, ascites or urine, kidneys small, pale, capsule slightly adherent, cut surface cloudy and apparently more fibrous than normal, liver and lungs congested, aorta apparently normal, heart not dilated, weight 55 gm

Microscopical Examination Moderate, diffuse, cellular proliferation of interstitial connective tissue which does not quite reach the surface in most places, capsule moderately thickened, relatively little glomerular change, some exudate but no cysts, marked parenchymatous change, little desquamation, much exudate, and many dense, hyaline casts

Protocol 18—Dog 26, 1910, a young pointer, received two injections of 50 mg of uranium nitrate with an interval of six and one-half weeks, and died seventeen weeks after the first injection, weight at beginning of experiment 20 5 kilos, weight at time of second injection 20 3 kilos, weight at time of death 12 kilos

Autopsy No subcutaneous edema or ascites Five c c urine showed a trace of albumin but no casts, kidneys normal size, pale, capsule slightly adherent, surface smooth cut surface cloudy, cortex appears rather reduced, liver, lungs and aorta normal, heart large, many subendocardial ecchymoses, no dilatation, weight 113 gm

Microscopical Examination Very marked cellular proliferation of interstitial connective tissue which is very diffusely distributed, kidney capsule markedly thickened, moderate glomerular change, much exudate and some small cysts, marked parenchymatous change, many tubules almost completely necrotic, moderate desquamation, much exudate and many dense hyaline casts In places there is cystic dilatation of some of the tubules

Protocol 19—Dog 27, 1910, a young mongrel male, received two injections of 40 mg of uranium nitrate with an interval of six and one half weeks, and died twenty-four weeks after the first injection, weight at beginning of experiment 13 8 kilos, weight at time of second injection 16 7 kilos, weight at time of death 12 kilos

Autopsy No subcutaneous edema and no ascites, 15 c c urine showed much albumin and sugar and many granular casts, kidneys swollen and pale, capsule thick and firmly adherent, surface torn and finely granular with some coarser nodules, cut surface opaque, cortex thin with evident strands of connective tissue extending outwards to the surface, liver cloudy, lungs congested, aorta apparently normal, heart large, right ventricle dilated

Microscopical Examination Very extreme proliferation of interstitial connective tissue which involves practically the whole of the cortex, and is everywhere very cellular, very marked glomerular change practically all glomeruli affected,

much exudate, proliferation and desquamation of capsular epithelium, and marked lobulation and shrinkage of tufts, a few glomeruli are hypertrophied, very extreme parenchymatous change in practically all tubules, with much dilatation of lumens, exudate, necrosis and desquamation, many tubules in areas of connective tissue proliferation are collapsed and atrophied, a few dense hyaline casts

In discussing the conclusions which seem justifiable from the foregoing experiments, it will be more convenient to make a division under three headings (1) edema formation, (2) renal changes, (3) cardiovascular changes

EDEMA FORMATION

The use of uranium nitrate as an irritant with which to produce kidney lesions in animals was suggested by the reports of Richter,[8] in which he described the production of edema in rabbits by the administration of uranium salts In my first series of experiments on guinea-pigs[1] varying amounts of ascites and hydrothorax were found in some cases, but in no instance was there any subcutaneous edema or general anasarca Pearce[6] referred to this fact during a discussion of the experiments, and he suggested that more complete analogy to human nephritis might have been obtained if rabbits had been used for injection instead of guinea-pigs, since it had been shown that edema was so readily produced in rabbits during acute uranium intoxication, but the more recent experiments have shown that this is not the case

In the series of sixteen experiments on rabbits which are here reported, but one animal showed any marked amount of fluid in the serous cavities, and only three others showed small amounts of ascites In none of the cases was there any subcutaneous edema It is true that three died of acute fibrino-purulent pleurisy, and that one showed a slight adhesive peritonitis, but these conditions were due to intercurrent infections and probably were in no way associated with any previous serous transudation

The guinea-pig experiments showed vastly different results[9] "In the complete series of seventeen animals which survived for longer than three months seven which died before the eighth month showed no edema, and of the ten which lived for longer than eight months, nine showed definite, and in some cases marked edema In four of the nine cases there was marked subcutaneous edema, which in three cases was associated with effusion into the serous cavities" All of the cases of subcutaneous edema occurred in animals to which relatively large doses of the drug had been administered, and, with one exception, in every case in which edema was present, the animal died within eleven days after the last injection

8 Richter Die experimentelle Erzeugung von Hydrops bei Nephritis Beitr z klin Med Festschr Herrn Prof Senator, Berlin, 1904, 283, and Experimentelle uber der Nierenwassersucht, Berl klin Wchnschr, 1905, xlii, 384

9 Dickson, E C Edema Formation in Guinea-pigs in Chronic Experimental Uranium Nephritis Proc Soc Exper Biol and Med, 1910, viii, 46

The significance of these observations on guinea-pigs is at least twofold In the first place, it is definitely proved that edema formation in animals resulting from the administration of uranium nitrate is not confined to rabbits and in the second place, a study of the conditions under which the edema was produced will show that there has been established a much closer analogy to the edema formation of Bright's disease in man

In the production of experimental uranium edema in rabbits by Richter,[8] Georgopulos,[10] Heinecke and Meyerstein[11] and others, the administration of uranium nitrate was always followed by forced water ingestion to produce an artificial hydremic plethora In the experimental production of edema by combining the action of renal and vascular irritants, Pearce[12] also forced water ingestion, and he established as the three requisites for the production of renal edema, kidney damage, vascular damage and hydremic plethora In my series of cases no attempt was made to induce edema by forcing water Throughout the experiment the animals were kept in a large cage from which they were removed from time to time for weighing and for further injections They were fed on a mixed diet in which was plenty of greens, and they obtained the whole of their water-supply from the green stuff which they consumed A hydremic plethora due to increased water ingestion is obviously impossible under such conditions, and one can only assume that the increase in the fluids in the body must have been due to the suppression of urine which occurred during the terminal attack of acute nephritis

The conclusion of all observers who have employed uranium salts for the experimental production of edema is that there must be some specific action of uranium in addition to its effect on the renal epithelium, which is at least partly responsible for the edema formation The observations of Heinecke and Meyerstein,[11] who found that edema was produced in rabbits which were poisoned with chromates only after the serum of rabbits suffering from acute uranium poisoning had been injected intravenously, were very suggestive, even though the results were not constantly produced, and there seemed to be sufficient ground for their conclusion that there must be some vascular damage, in addition to the renal damage, which was responsible for the edema formation The oncometer experiments of Schlayer and Hedinger[13] and Takayasu[14] gave

10 Georgopulos Experimentelle Beitrage zur Frage des Nierenwassersucht Ztschr f klin Med, 1906, lx, 411

11 Heinecke and Myerstein Experimentelle Untersuchungen uber die Hydrops bei Nierenkrankheiten Deutsch Arch f klin Med, 1907, xc, 101

12 Pearce The Production of Edema, an Experimental Study of the Relative Etiologic Importance of Renal Injury, Vascular Injury and Plethoric Hydremia THE ARCHIVES INT MED, 1909, iii, 422

13 Schlayer and Hedinger Experimentelle Studien uber toxische Nephritis Deutsch Arch f klin Med, 1907, xc, 1

14 Schlayer, Hedinger and Takayasu Ueber nephritisches Oedem Deutsch Arch f klin Med, 1907, xci, 59

the first experimental proof that such must indeed be the case, and their observations have been confirmed by Pearce and his assistants [15] Pearce[12] has further established the importance of vascular injury in renal edema in the series of experiments to which I have already referred, namely, those in which he employed combinations of various vascular irritants with bichromate poisoning and forced water ingestion

In view of these uniform conclusions as to the importance of damage to the blood-vessels in the production of renal edema, but one explanation can be given for its occurrence in the cases here described The fact that the death of the animals and the onset of the edema occurred during the acute intoxication which followed the last injection of uranium, indicates definitely that the edema was a true renal edema, and not edema due to failing compensation of an overworked heart, and the appearance of the hearts at autopsy confirmed this view There must therefore have been some condition present after the several months of treatment, which rendered the animals unable to cope with the hydremia of an acute attack of nephritis which was presumably no more severe than that of any one of the several previous attacks It is difficult to see how this condition could be other than some damage to the smaller blood-vessels, especially in those cases in which the subcutaneous edema was so well developed I believe we are justified in concluding that the repeated injections of uranium had so acted on the (blood) vascular system that it was no longer able to withstand the increase in the volume of blood which results from the partial or complete suppression of urine of acute uranium poisoning

Whether or not this be the correct explanation, there can be no doubt that the formation of edema, occurring as it did in these animals during an attack of nephritis, and without any artificially produced hydremic plethora, establishes another step in the advance toward a complete analogy to Bright's disease in man

RENAL CHANGES

The histological appearance of chronic uranium nephritis has already been described in the beginning of this report, and the characteristic type of the lesions, as well as the constancy with which they occur, has been mentioned In order to determine whether similar lesions of spontaneous origin occur in normal animals a series of routine histological examinations was made of the kidneys of fifty rabbits and 100 guinea-pigs which had been sacrificed for various purposes in the laboratory The results of these observations have recently been reported by Ophuls,[16] from whom I shall quote the following

15 Pearce, Hill and Eisenbrey Experimental Acute Nephritis, the Vascular Relations and the Elimination of Nitrogen Jour Exper Med, 1910, xii, No 2, 196

16 Ophuls W Occurrence of Spontaneous Lesions in Kidneys and Livers of Rabbits and Guinea-Pigs Proc Soc Exper Biol and Med, 1911, viii, 75

In view of the importance of the occurrence of spontaneous lesions in the kidneys and in the livers of rabbits and of guinea-pigs in reference to the experimental work on these organs, Dr E C Dickson and myself have made a careful study of these organs and incidentally of the heart and of the aorta in fifty rabbits and in one hundred guinea-pigs The animals used were partly fresh animals from the market, partly animals raised at the laboratory * * *

Twenty eight rabbits, among them some of the old ones, had entirely normal kidneys, nine showed slight parenchymatous lesions, three a few small areas of cellular infiltration In ten we found scattered small areas in which were marked interstitial lesions with the formation of small depressions on the surface Four of these proved to be radially arranged chronic septic foci which extended from the vicinity of the papilla to the outer surface In the other six cases the same arrangement of the newly-formed connective tissue in narrower radial bands which start deep in the pyramids was noticeable although no evidence of a septic infection could be discovered The interstitial lesions were accompanied by marked epithelial lesions in two cases only, producing to a certain extent the picture of a chronic parenchymatous nephritis, although the lesions were never very extensive Lesions of the blood-vessels or primary lesions of the glomeruli were not found in any case * * *

Of the one hundred guinea-pigs the large majority had been injected with sediment from urine or other material suspected of containing tubercle bacilli only a few actually developed tuberculosis There were several especially selected old animals Sixty-three of the one hundred had absolutely normal kidneys, two showed slight parenchymatous lesions and in thirty-five there were scattered small areas of cellular infiltration in the cortex which were sometimes rather numerous, at other times they were found with difficulty only on careful examination of several sections They consist largely of lymphocytic cells and a few larger cells with vesicular nuclei They do not seem to have much tendency to develop into fibrous tissue although occasionally such a change was observed but always to a limited degree only * * * In few cases fibrous thickening of the capsules of glomeruli and cystic dilatation of the same were observed as spontaneous lesions similar to certain types of glomerular cysts described by Dickson in his paper on the "Experimental Production of Chronic Nephritis in Animals By the Use of Uranium Nitrate" These were however, rare exceptions, whereas in uranium poisoning such glomerular lesions seem to be nearly constant Large scars or lesions of the blood-vessels were not found in any case

It will be seen from this extract that, although there was a fairly high percentage of cases which showed spontaneous kidney lesions, the type of the lesions which were found was entirely different from that of chronic uranium nephritis Indeed, in some of the rabbits of my series there was quite evidently a combination of the two conditions, for in kidneys which were distinctly of the uranium type a few scattered foci could be recognized as more closely resembling the spontaneous type of lesions And, moreover, although the spontaneous lesions which were found in the kidneys of rabbits were entirely different from those which were found in guinea-pigs, the lesions which were produced by uranium in both rabbits and guinea-pigs, and indeed also in dogs, were so similar as to be almost identical in many cases

In the dog experiments, too, care was taken to exclude as much as possible the occurrence of spontaneous chronic kidney lesions Young, healthy animals were always selected for experimentation, and of the nineteen cases here reported fifteen were known to be less than 9 months

of age at the time of the first injection In the 1909 series, Protocols 1 to 5,[17] especial precautions were taken to preclude the possibility of the development of spontaneous lesions Puppies were weaned in the laboratory and were placed on a diet consisting of mush, bread and milk, with an occasional feeding of dried, chopped meat from which the extractives had been removed in the soup-pot The animals thrived on this diet and received no other food during the whole course of the experiment When they were 5 months old the series of injections of uranium nitrate were commenced, and, with the exception of one animal which was killed in a fight fourteen weeks after injection, they were allowed to live for from twenty-seven to thirty-four weeks after the first injection The oldest of these puppies was 11½ months old when killed, so that in every case the experiment was terminated within the first year of life of the animal The carefully regulated diet was such that the kidneys were protected as much as possible from the influence of any irritating substance excepting the uranium nitrate, and, when we consider in addition to this that in every case the animal was less than 1 year old at the end of the experiment, there seems little doubt that the lesions which were found must have been due to the administration of the uranium nitrate Further experiments have confirmed this conclusion, for in the whole series of dogs which were observed during the following eighteen months not one animal failed to show kidney lesions of a chronic nature, and of the uranium type, excepting those which died during the initial acute intoxication The experiments show definitely that dogs are well adapted for the production of chronic kidney lesions, and that these lesions may be produced in practically all cases by the administration of uranium nitrate

Although the occurrence of the chronic lesions in the kidneys has been so constant, the method by which these lesions are produced has not been revealed A very striking feature of chronic uranium nephritis is that, even in the advanced cases in which the kidneys are hard and granular, and in which the greater part of the parenchyma is replaced by dense fibrous tissue, there is no demonstrable lesion in the vessels of the kidneys or of the peripheral vascular system It is true that in many cases, especially in dogs, there is a peculiar peri-arterial development of fibrosis, and that in rabbits many of the glomerular tufts show almost complete fibrosis, but in the capillaries of these tufts the only evidence of lesion is a slight thickening of the walls, and the deposit of some hyaline substance around them, and in the larger arteries no lesions whatever can be demonstrated either in the intima or in the media This fact is especially interesting in view of the recent experiments of Harvey[18] who, by the

17 The 1909 series of experiments on dogs was reported before the California Academy of Medicine in December, 1909 Cal State Jour Med, 1910, viii, No 4, 140

18 Harvey Auto intoxication and Experimental Nephritis in Rabbits Jour Path and Bact, 1911, xvi, No 1, 95

administration of para-hydroxy-phenyl-ethylamine, was able to produce chronic lesions in the kidneys of rabbits secondarily to the development of atheroma of the aorta and arteriosclerosis of the renal artery and its branches The kidneys which Harvey describes are undoubtedly of the arteriosclerotic type, and his experiments would seem to prove that the etiology of that type of nephritis is entirely different from that of such types of atrophied and granular kidneys as are represented by uranium chronic nephritis

Another point of interest in these cases is one to which I referred in my previous report In the kidney lesions of acute uranium poisoning the tubular epithelium is the part which shows the most marked anatomical change With the exception of the formation of the hyaline bodies which Christian[3] has described in the glomerular tufts during acute uranium nephritis, no characteristic lesions have been found in the glomeruli, yet in the kidneys of chronic uranium nephritis the glomerular lesions are varied and severe The most common, as well as the most extensive changes, are seen in the glomerular capsule, with its cystic dilatation, proliferated epithelium and hyaline basement membrane The tufts also are more or less extensively damaged In the less severe cases we find fragmentation of the nuclei and often some evidence of increase in connective tissue cells, and in the advanced cases there is distinct fibrosis and lobulation of the tufts, and, in rabbits, the thickening of the walls of the capillaries and the deposit of some hyaline substance in a part or the whole of the tufts, to which reference has already been made Moreover, the compensatory hypertrophy of the more normal appearing glomeruli indicates diminution in function of the damaged glomeruli

Still another interesting feature in chronic uranium nephritis is the characteristic distribution of the newly formed connective tissue In every case it is more marked and much more fibrous in the inner zone of the cortex, and in the early cases it is in this region, especially around the larger blood-vessels, that the proliferation of connective tissue is first seen Reference has already been made to the peculiar peri-arterial fibrosis which occurs around the larger arteries From this deeper, more fibrous zone, the connective tissue extends outward toward the surface of the kidney, usually following the lines of the medullary rays In those cases in which the surface of the kidney is granular, the processes extend to the surface and correspond to the small depressions on it, but in many cases where the surface is still quite smooth histological examination shows in the deeper parts much newly formed connective tissue from which many radiating processes extend into the outer zone of the cortex but do not reach the surface In some kidneys there is also a diffuse connective tissue proliferation which more or less completely destroys the kidney cortex between the rays, but this seems to be a later stage in the process and is found only in the most severe cases Occasionally there is also a

more or less marked extension of the connective tissue proliferation into the medulla, but this is not at all constant

A very striking feature of the connective tissue proliferation is that all the different stages are represented in the kidneys of animals which have not received any injections for several months The condition is not that of a quiescent scar formation, for, although in the deeper portions the newly formed connective tissue is densely fibrous and contains but few nuclei, in the peripheral portions it is usually very cellular, with many spindle shaped cells with large, clear vesicular nuclei, and with many round plasma cells, clearly indicating that the connective tissue proliferation is still progressive Only in those cases in which the kidney is markedly shrunken and granular does the peripheral portion of the connective tissue have a dense fibrous structure, and even in these there are usually scattered areas of cellular infiltration in which the cells consist partly of fibroblasts and partly of plasma cells

The explanation of these phenomena is not clear At first sight it might seem that the extreme degeneration and necrosis of the tubular epithelium in acute uranium poisoning must be responsible for the secondary proliferation of the connective tissue and for the marked glomerular changes If we accept the teaching of Senator, namely that destruction of any part of a tubule system will lead to secondary destruction of the remainder of that tubule system, we could explain the destruction of the glomeruli, and, perhaps also, the cystic dilatation of the glomerular capsules But it is difficult to understand how simple destruction of the tubular epithelium could account for the peculiarly constant development of connective tissue in the inner zone of the cortex, or for the evident progression of the connective tissue proliferation which is found months after the insult which produced the primary necrosis. Again, if it is simply the epithelial necrosis which is responsible, one would expect to find equally severe secondary fibrosis in kidneys which have been poisoned with potassium bichromate, for in acute bichromate nephritis the lesions are practically indistinguishable from those which are produced by uranium nitrate The experiments of Ophuls seem to show that this is not the case He subjected forty guinea-pigs and fifty rabbits to repeated injections of potassium bichromate during periods varying from a few weeks to almost two years' duration In his recent report[19] on the effects produced in guinea-pigs he says

> The conclusion seems justified that it is impossible to produce severe lasting lesions in guinea-pigs with chromates, probably because in these animals the chromates are too toxic in a general way, and too slightly effective on the kidneys locally

19 Ophuls, W Experimental Nephritis in Guinea-Pigs by Subcutaneous Injections of Chromates, Proc Soc Exper Biol and Med, 1911, ix, 13

And in describing his experiments on rabbits he says [20]

Rabbits are relatively more susceptible to the action of chromates than guinea-pigs * * The extreme lesions which may develop after a while as a result of crowding of large doses were described by me in 1908 (*Journ Med Research*, 1908, xviii, 49), but they do not necessarily follow even repeated administration of large doses * * * Fifty animals were experimented upon The dosage varied between two centigrams and two milligrams Some of the animals were kept alive for a year or more So far as epithelial lesions are concerned the experiences are similar to those in guinea pigs, except that the epithelial lesions became more severe and seemed to continue longer after the last injection Very marked interstitial lesions were observed at times, but they resemble those observed spontaneously so closely, and occurred so irregularly, sometimes soon, sometimes late after the administration of various doses and sometimes not at all, that any definite conclusion of their relation to the injections could not be arrived at

It is true that the findings of Smith[2] differ considerably from those described by Ophuls From a series of thirty-nine rabbits and seven guinea-pigs which survived for longer than three months after the initial injection of either potassium bichromate or uranium nitrate (the exact number of each is not stated), he concludes that "the chronic lesions caused by uranium nitrate and potassium bichromate were the same." and that "bichromate of potassium produces more fibrous tissue formation with macroscopic depressions on the surface of the kidney than uranium nitrate"

If these observations of Smith are based on a sufficiently large number of cases of bichromate nephritis, his results are of great interest in view of the large number of negative results described by Ophuls, and they would greatly weaken the argument that in uranium nephritis it is not alone the epithelial necrosis which is responsible for the secondary development of fibrous tissue However, judging from the large number of experiments which have been conducted in our laboratory, there seems little doubt that in uranium nitrate nephritis there is some factor which is lacking in potassium bichromate nephritis, and which is responsible for the almost constant production of chronic kidney lesions in the former Just what this factor may be is still in doubt I am convinced that there is something more than mere coincidence in the fact that there is the occurrence of edema in acute uranium intoxication, and the development of chronic kidney lesions after prolonged uranium administration If it be true that the formation of edema depends on a combination of lesions in the kidneys and in the peripheral blood-vessels, I believe there is no doubt that the development of the chronic kidney lesions is dependent on a similar combination of lesions Indeed, I believe that no other condition than some damage to the vascular system can explain

20 Ophuls, W Experimental Nephritis in Rabbits by Subcutaneous Injections of Chromates Proc Soc Exper Biol and Med, 1911, ix, 13

the peculiarly characteristic distribution and the progressive type of interstitial connective tissue proliferation which we find in chronic uranium nephritis

THE CARDIOVASCULAR CHANGES

The question of the interrelationship which exists between hypertrophy of the left ventricle of the heart and chronic interstitial nephritis is one which has received much attention Various observers have approached the problem by simulating the local kidney conditions of chronic interstitial nephritis by the actual reduction of kidney substance by surgical methods Bradford,[21] Passler and Heinecke,[22] Janeway,[23] Sampson and Pearce[24] and others have found that, following such reduction of kidney substance, there develops in certain cases a rise in blood-pressure and hypertrophy of the left ventricle of the heart Rautenberg[25] also by mechanically damaging one kidney and subsequently removing the other kidney has succeeded in raising blood-pressure in rabbits to such an extent that aneurysms of the aorta are formed But the number of observations of development of hypertrophy of the heart in cases of experimental chronic nephritis is very small Charcot and Gombault[26] and Levaditi[27] report hypertrophy of the left ventricle of the heart in cases of experimental chronic nephritis produced by lead salts and vinylamin, respectively Siegel[28] reports hypertrophy of the left ventricle of the heart in three dogs which had been subjected to uranium injections for from three to six weeks, and Smith[2] reports four cases of apparent heart hypertrophy in his series of uranium nitrate rabbits However, the limited number of instances in which experimental chronic nephritis has been produced has of necessity limited the number of observations which could be made

In a series of experiments such as those reported in this paper the difficulty of determining the presence of a true heart hypertrophy is very

21 Bradford The Results following Partial Nephrectomy, and the Influence of the Kidney on Metabolism Jour Physiol, 1899, xxiii, 415

22 Passler and Heinecke Versuche zur Pathologie des Morbus Brightii Verhandl d deutsch pathol Gesellsch, 1905, ix, 99

23 Janeway Note on Blood-Pressure Changes Following Reduction of the Renal Arterial Circulation Proc Soc Exper Biol and Med, 1909, vi, 109

24 Sampson and Pearce A Study of Experimental Reduction of Kidney Tissue with Special Reference to the Changes in That Remaining Jour Exper Med, 1908, x, 745

25 Rautenberg Erzeugung chronischer Nierenkrankungen mit folgender Blutdrucksteigerung und Arteriosklerose Deutsch med Wchnschr, 1910, xxxvi, 551

26 Charcot and Gombault Noté relative à l'Étude anatomique de la néphrité saturnine expérimentale Arch de physiol, 1881, Series 2, viii, 126

27 Levaditi Experimentelle Untersuchungen uber die Necrose der Nierenpapillæ Arch internat de pharmacodyn, 1901 viii, 5

28 Siegel Uber experimentelle Nephritis Verhandl d Congresses Inn Med, 1907, xxiv, 217

great In normal animals quite definite ratios of heart to body weight have been established, and in animals which have been subjected to experimentation but in which the weight at the time of death shows no marked variation from the weight during the time in which the animal has been under observation, similar heart to body ratios can be established and compared with those of normal animals But in those animals which lose in weight during the course of the experiment, and especially in animals which decrease rapidly in weight during the terminal illness, such heart to body ratios are difficult to determine One cannot tell exactly what proportional loss of weight occurs in the heart itself during the progressive loss in the whole body weight, in such cases one must rely largely on the macroscopic appearance of the heart In well-marked cases of heart hypertrophy there is little difficulty in forming an opinion, but in doubtful cases, and especially in the smaller animals, one must be very guarded in making the decision that hypertrophy actually exists

Conservative inspection of the hearts of the animals reported in this paper showed quite definitely that there was hypertrophy of the heart, especially of the left ventricle, in two guinea-pigs, four rabbits and nine dogs In several other cases the heart gave one the impression of being hypertrophied, but the hypertrophy, if present, was too slight to justify a definite conclusion In the rabbits and guinea-pigs no confirmatory heart to body ratios were established, but in the dogs such ratios were determined and were studied in comparison with those worked out in normal dogs by Stewart[29] and Joseph [30] Table A shows clearly the result of this comparison

In Stewart's series of twenty normal dogs he found that there was an average heart to body ratio of 0 00724, a ratio approximately the same as that obtained by Joseph, namely, 0 00750 But among Stewart's twenty animals there were three which showed a ratio of 0 00800 or over, and in his series of experiments he withheld a diagnosis of heart hypertrophy in all cases in which the ratio did not exceed the maximum ratio obtained in his normal dogs It will be seen that some of my cases fall below the maximum normal ratio as estimated by Stewart, and may therefore be viewed with some suspicion But when we consider that in all my cases the animals were confined to small quarters during practically the whole of their lifetime, and would presumably on that account show relatively smaller hearts than would active street dogs, the constantly high ratio is very striking And it is of interest that my three normal controls, which were kept under similar conditions, all showed heart to body ratios which were well below the average as established by Stewart It is also

29 Stewart An Experimental Contribution to the Study of Heart Hypertrophy Jour Exper Med, 1911, xiii, 187

30 Joseph The Ratio between the Heart Weight and the Body Weight in Animals Jour Exper Med, 1908, x, 521

of interest that in all but two of the cases included in the accompanying table, the weight at the time of death was as great or greater than at any time during the course of the experiment, due to the fact that these animals were intentionally or accidentally killed several weeks after the last injection In two cases in which there was definite loss of body weight immediately preceding death, the ratio of the heart weight at the time of death to the maximum body weight during life was high, and I believe that one is justified in assuming that the actual heart to body ratio must lie somewhere above that ratio, but below the ratio of the heart weight at time of death to the body weight at time of death Accordingly in the table these two ratios are entered as (a) and (b) and the actual heart to body ratio is assumed to lie somewhere between the two, in both cases at a point which is high as compared with the average normal ratio

TABLE A.—(A) SHOWING THE RATIOS WHICH EXIST BETWEEN THE HEART WEIGHT AND THE BODY WEIGHT IN DOGS WITH CHRONIC URANIUM NEPHRITIS, (B) SHOWING SIMILAR RATIOS IN NORMAL DOGS

Protocol Number	Animal Number	Duration of Exp't, Weeks	Body Weight in Grams	Heart Weight in Grams	Ratio
2	3—1909	34	10,260	80	0 00779
3	4—1909	31	14,280	118	0 00802
5	6—1909	29	5,610	60	0 01069
6	1—1910	61	7,680	61 5	0 00800
7	2—1910	71	16,300	145	0 00888
8	3—1910	60	21,600	180	0 00818
9	5—1910	25	(a) 8,980	73	0 00822
			(b) 8,020	73	0 00922
17	24—1910	32	(a) 6,900	55	0 00790
			(b) 5,200	55	0 01041
			NORMAL CONTROL ANIMALS		
	8—1909		8,640	60	0 00694
	4—1910		8,400	60	0 00714
	29—1910		4,680	34	0 00705
Stewart's Series—20 dogs					0 00721
Joseph's Series					0 00750

These weights and ratios are presented with the full realization that in some of them the proportional weight of the heart is somewhat below what may be considered the limit of normal variation However, I believe that when we take into consideration the age of the animals which were used, the conditions under which they were kept, and the fact that in every case the heart showed macroscopic appearance of hypertrophy, one is justified in presenting them as evidence of proportional increase in the size of the heart

The condition of the blood-vessels has already been described in considering the lesions which are found in the kidneys.

CONCLUSIONS

1 By the administration of uranium nitrate it is possible to produce a chronic diffuse nephritis in guinea-pigs, rabbits and dogs

2 The histological picture of the lesions is characteristic, and is analogous to, but not identical with, that found in chronic diffuse nephritis in man

3 The chronic lesions, even in the most severe cases, are not associated with demonstrable arterial lesions, although the mode of development suggests that there must be some functional vascular damage

4 After prolonged administration in guinea-pigs a terminal attack of acute nephritis is frequently accompanied by more or less marked anasarca

5 Associated with the more severe kidney lesions there is frequently a more or less marked hypertrophy of the left ventricle of the heart

Sacramento and Webster Streets

AN EXPERIMENTAL STUDY OF THE CHANGES IN THE BLOOD FOLLOWING SPLENECTOMY

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In reviewing[1] recently the literature of splenectomy I was impressed with the very considerable variations in the cytology of the blood following the removal of the spleen in both man and animals As this difference could not be explained by clinical history in the one case nor by experimental conditions in the other, a study of the changes in the dog's blood consequent on splenectomy was undertaken

The literature of the subject is somewhat voluminous and may therefore be reviewed in two ways first from the point of view of physiological and experimental observation and second on the basis of clinical observation At present the function of the spleen in relation to the formation or destruction of blood-cells is not definitely known Howell[2] states that the spleen is supposed to be the place of origin of erythrocytes This is true in fetal life and shortly after birth but we have no proof that this function is preserved at later periods The presence of a large amount of iron suggests that the spleen may have a function in preparing hemoglobin This view is strengthened by the fact that after splenectomy there is an increase in daily loss of iron[3] That the spleen is the graveyard of erythrocytes, a theory founded on histological evidence that is, the presence of broken down and partially destroyed red blood-cells, Howell believes, has not been satisfactorily demonstrated He believes also that the spleen has but small part in the formation of leukocytes Flint[4] states that "it may be that the spleen destroys a certain number of red corpuscles and that it also produces new red blood-corpuscles" He also says that excision of the spleen causes a diminution in the number of erythrocytes, and an increase in the proportion of leukocytes Ott[5] states briefly that the spleen is supposed to manufacture erythrocytes while Stewart[6] makes no comment on the relation of the spleen to the blood

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1 Musser, J H, Jr Cysts of the Spleen, Am Jour Med Sc, 1911 cxlii 501

2 Howell W H Text-Book of Physiology, Saunders Phila, 1911 Ed 4

3 Grossenbacher and Asher L Zentralbl f Physiol, 1908 xii 121

4 Flint, Austin Jr Text-Book of Human Physiology Appleton New York 1888 Ed 4

5 Ott Isaac Text-Book of Physiology, Davis Phila, 1907 Ed 2

6 Stewart Manual of Physiology Wood & Co New York, 1910 Ed 6

Neither of these last authors has anything to say concerning the effect of extirpation of the spleen Fredericq and Nuel[7] dismiss the subject of excision of the spleen by merely saying that it causes an increase in lymphoid tissue

Extirpation of the spleen in experimental animals has given widely varying results Apparently the first effort to study the blood of splenectomized dogs was that of Picard and Malassez[8] in 1878 The investigators concluded that splenectomy diminishes the amount of hemoglobin but not the number of red blood-cells Since then further studies of the blood changes have given various results Thus, Vulpius[9] found a marked increase in the number of leukocytes averaging between 21,000 and 26,000 for the first forty days — no count being made of the first day — and then gradually falling and reaching normal about the sixty-fifth day The erythrocytes on the other hand, fell at first to about 4,000 000 but returned to normal about the fiftieth day A decrease in hemoglobin was found also, but to what extent and how long is not stated

Gibson[10] found in two dogs a decrease in the erythrocytes lasting until the 107th day the period of greatest diminution corresponding to the sixtieth and sixty-fourth days, respectively In a third dog but little change was observed, the lowest count being on the ninetieth day In one dog he found a leukocytosis lasting for three weeks

Laudenbach's[11] experiments showed a decrease in erythrocytes and hemoglobin and an increase in leukocytes In two dogs the maximum decrease in hemoglobin and red cells occurred on the seventy-seventh day and in the third dog on the 103d day The decrease of hemoglobin was in the first two dogs 20 per cent and 55 per cent respectively, and of red blood-cells about 1,000 000 and 2,500,000 respectively The third dog presented the picture of a pernicious anemia, hemoglobin dropping to 20 per cent, the red cells to about 1 000,000 on the 103d day, after this period the anemia became somewhat less severe, but the animal died a short time afterward Laudenbach quotes Zezas as saying that in wolves, after splenectomy the greatest decrease in red blood-cells occurs in the second week Vinogradoff[12] finds this to occur on the 200th day in dogs

Other investigators[13] state that the removal of the spleen in dogs has no effect on the number of blood-corpuscles A leukocytosis which they

7 Fredericq L, and Nuel, J P Eléments de Physiol Humaine, Masson, Paris, 1904

8 Picard, P, and Malassez Gaz méd de Paris 1878, viii, 185, Series 5

9 Vulpius Oskar Beitr zur Klin Chir, 1894, xi 633

10 Gibson J L Jour Anat and Physiol, 1886, xx, 324

11 Laudenbach J Arch d Physiol, 1897 ix 385

12 Vinogradoff Quoted by Emile Bordet, Thèse de Paris 1897

13 Paton, D N, Gulland, G L and Fowler, J S Jour Physiol 1902, xxviii 83

find, and which reaches its height about the fourth week, they attribute to a slight suppuration originating at the time of operation

Nicholas and Dumonhim[14] found a postoperative leukopenia followed by an eosinophilia and a lymphocytosis

Three standard works on hematology give the results of splenectomies in man, as follows

DaCosta [15] "Excision of spleen in man is followed by a diminution of hemoglobin and red blood-cells Blood regeneration is slow, taking one to three months There is also a leukocytosis of the polyneutrophil type of from 15,000 to 30,000, persisting for four to six weeks After some months or a year or two, eosinophilia develops Lymphocytosis is a frequent but unconstant condition"

Cabot[16] says that after splenectomy occurs a hyperplasia of lymph-nodes associated with a lymphocytosis, later a moderate eosinophilia with an increased number of mast cells Grawitz[17] says that in man there is no especial change in the red blood-cells, showing therefore that the spleen has nothing to do with the regeneration of the red blood-cells Most striking, in many cases, are the alterations in the leukocytes, in man, as well as in animals, after splenic extirpation, an increase of lymphocytes, and also of eosinophils is common

In considering the results of splenectomy in man, the blood examinations in most of the reported cases must be discounted or completely discarded as the operation was one for some consideration of (1) the spleen as an abscess or a rupture with slow hemorrhage or (2) of the blood, as in Banti's disease, which, *a priori*, would alter the blood-picture Again, in some of the chronic conditions the spleen may have been diseased so long and so extensively that a vicarious compensation of its function by other organs may have occurred, thus obscuring the effect of removal Therefore in reviewing the literature of splenectomy such cases have as a rule been omitted

The case under the author's observation, and the immediate cause of this investigation, was an individual with a cyst of the spleen Before operation the blood examination was normal except for some slight anemia Eight days after operation it was as follows

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14 Nicholas, J, and Dumonhim, L E and F Jour de physiol et de path gén, 1903, v, 1073

15 DaCosta, John C, Jr Clinical Hematology, Blakiston, Phila, 1905, Ed 2

16 Cabot, R C Clinical Examination of Blood, Wood & Co, New York, 1904, Ed 5

17 Grawitz, E Klin Pathologie des Blutes, Thieme, Leipzig, 1906, Ed 3

Erythrocytes	4,642,000	
Hemoglobin	90	per cent
Leukocytes	11,400	
Polymorphonuclears	70 6	per cent
Lymphocytes	14 6	per cent
Large mononuclears and transitionals	12 2	per cent
Eosinophils	2 4	per cent
Basophils	0 2	per cent
After eighteen days		
Erythrocytes	3,916,000	
Hemoglobin	87	per cent
Leukocytes	13,900	
Polynuclears	60	per cent
Lymphocytes	24	per cent
Large mononuclears and transitionals	16	per cent
After nine months		
Erythrocytes	4,400,000	
Hemoglobin	80	per cent
Leukocytes	17,000	
Polymorphonuclears	70	per cent
Lymphocytes	25	per cent
Large mononucleais and transitionals	4	per cent
Eosinophils	0 5	per cent
Undetermined	0 5	per cent
After fifteen months		
Erythrocytes	4,220,000	
Hemoglobin	75	per cent
Leukocytes	14,800	
Polynuclears	58	per cent
Lymphocytes	38	per cent
Large mononuclears and transitionals	9	per cent
Basophils	1	per cent
Eosinophils	1 5	per cent
Undetermined	0 5	per cent

Henricius[18] in a similar case found a diminution of about 500,000 red blood-cells, 20 per cent hemoglobin and an increase of leukocytes to 19,800 Five months later the leukocytes were 13,200 and seventeen months later, 12,000 In a case of splenic anemia reported by Warren[19] a hemoglobinemia existed at time of operation, the hemoglobin was 65 per cent, red blood-cells were normal and the leukocytes 2,200 Immediately after operation occurred an increase of white cells and a gradual fall of red cells and coloring matter On the sixteenth day after operation the red cell count was 3,256,000, hemoglobin 45 per cent and the leukocyte count 24 000 Eight days later the hemoglobin was 40 per cent, leukocytes 21,000 and red blood-cells 4,632,000 Hartmann[20] and Vaquez report several cases of excision of a spleen, one of which was on account of a twist of the pedicle The record of one of their cases shows that the red blood-cells fell to 1,634,000, hemoglobin to 45 per cent, and the leukocytes rose to 17,000. A year later the hemoglobin and erythrocytes were practically normal and the leukocytes numbered 27,000 Another case

18 Henricius Arch f Klin Chir, 1904, lxxii, 138

19 Warren, J C Ann Surg, 1901, xxxiii, 513

20 Hartmann and Vaquez Compt rend Soc de Biol 1897, iv, 126

mentioned by them showed one month after operation a loss of 1,500,000 red blood-cells and an increase of leukocytes to 18,000 A year later the red blood-cells had only slightly increased, the hemoglobin was normal and the leukocytes markedly increased Three years after operation a pronounced secondary anemia developed with a leukocyte count of 20,000 Swaim[21] reports a case in which the patient operated on for a simple hypertrophy of the spleen showed no blood changes before operation After a few days the red blood-cell count was 2,160,000 while the leukocytes numbered 23,800 Before the discharge of the patient the red blood-cell count returned to normal and the leukocytes to 16,250 Monnier,[22] in a case of cyst of the splen, found the leukocyte count before operation to be 7,000 and two months later 13,000

Myers[23] in a careful study of the blood found the red blood-cells and hemoglobin to be low after splenectomy but gradually increased as time went on The leukocytes also rose, reaching 28,400, and two months after operation were still high (14,100) The differential count showed a rather marked lymphocytosis

Jepson[24] quotes a case in which the erythrocytes fell from 5,000,000 to 3,300,000 but after three weeks returned to 4,500,000 The leukocytes increased from 6,000 to 27,000 Heaton[25] found no change at all in the blood except a great increase of large mononuclear and transitional forms Eliot,[26] in a case of splenectomy for rupture of the spleen, found one year after operation a leukocytosis of 17,000, hemoglobin 95 per cent and red blood-cells 5,800,000 In a second case, Staehelin's,[27] of rupture, the greatest leukocyte count was on the ninety-fifth day, the lowest hemoglobin on the 128th day and the lowest red blood-cell count on the 161st day

These isolated observations have been selected from many reports which in general show about the same blood-picture The reports have for the most part been made to indicate the results of splenectomy as an operative procedure rather than an account of the blood-picture A general analysis, however, shows that in the majority of cases a marked leukocytosis is present and persists for a year or more, often a pronounced secondary anemia occurs, in which the color index is normal as a rule, so also lymphocytosis without much change otherwise in the differential count However, as has been emphasized, in a small minority of the cases these changes are not found, a fact which explains the variation in the blood-picture, which at first sight seemed so remarkable

21 Swaim, James Bristol Med Jour, 1910, xxviii, 223
22 Monnier, E Beitr z klin Chir, 1904, xli, 181
23 Myers, Jerome Jour Am Med Assn, 1909, lii, 1231
24 Jepson, W Jour Am Med Assn, 1905, xlv, 690
25 Heaton, George Brit Med Jour, 1899, ii, 476
26 Eliot, E, Jr Tr Am Surg Assn, 1907, xxv, 336
27 Staehelins, R Deutsch Arch f klin Med, 1903, lxxvi, 364

In the present series of observations three dogs were employed, the results with these were so uniform that further study was considered unnecessary Healthy adult dogs were selected and preliminary counts of the blood of each of the animals were made before operation The splenectomies were performed as rapidly as possible under ether anesthesia and with rigid aseptic precautions, with practically no hemorrhage and without any untoward after effects After operation the blood counts were made daily for five days, then every other day for a week, then every fourth day, every week, later on every two weeks and finally every third week The counts were all made in a uniform manner at the same time of day and the same number of hours after feeding (see accompanying table)

Normal dog's blood, as might be expected, differs somewhat from that of man The normal red cell count varies between 4,500,000 and 6,500,000 and the hemoglobin bears a proportional relation The leukocytes vary from 8,000 to 15,000 with an average of 11,400 per millimeter

The differential count also shows some slight variations Busch and Van Bergen[28] found in the dog five types of leukocytic cells as follows: polynuclears 65 7 per cent, lymphocytes 21 per cent, large mononuclears 6 8 per cent, eosinophils 5 3 per cent, mast cells 1 2 per cent

The dogs of the present series all showed preliminary normal counts in accordance with these figures After operation the most striking changes were in the leukocytes, hemoglobin and red blood-cells (Charts 1 and 2) The hemoglobin and red blood-cells showed a gradual progressive and an almost proportional drop until the twenty-sixth day after operation This was more marked in Dog 1, whose hemoglobin fell to 50 per cent and red blood-cells to 2,800,000 In Dog 2 the fall was less marked, the figures being 65 per cent and 3,500,000, respectively The figures for Dog 3 were midway between the other two From the twenty-sixth day to the eighty-second day a constant increase of the red cells and hemoglobin was found Since that period and until the 138th day the counts remained practically normal or a little below normal The leukocytes showed a great increase immediately after operation This was most marked in Dog 2, which had a leukocytosis of 48,000 twenty-four hours after operation, at forty-eight hours the count fell considerably and from then on gradually returned to normal Dog 3 showed a slight leukocytosis as compared with that of the other two dogs On the fourteenth day the leukocyte count was below 15,000, there it remained until the last counts when it was found to have risen somewhat The differential count showed nothing very definite The polynuclear count was at various times either high or low, when it was high the lymphocyte

28 Busch, F C, and Van Bergen, C Jour Med Research, 1902, viii, 408

count was low, and vice versa For the most part the former remained higher than in the normal dog A rather striking change was found in the eosinophils At first occurred a slight rise in the proportion of

Chart 1

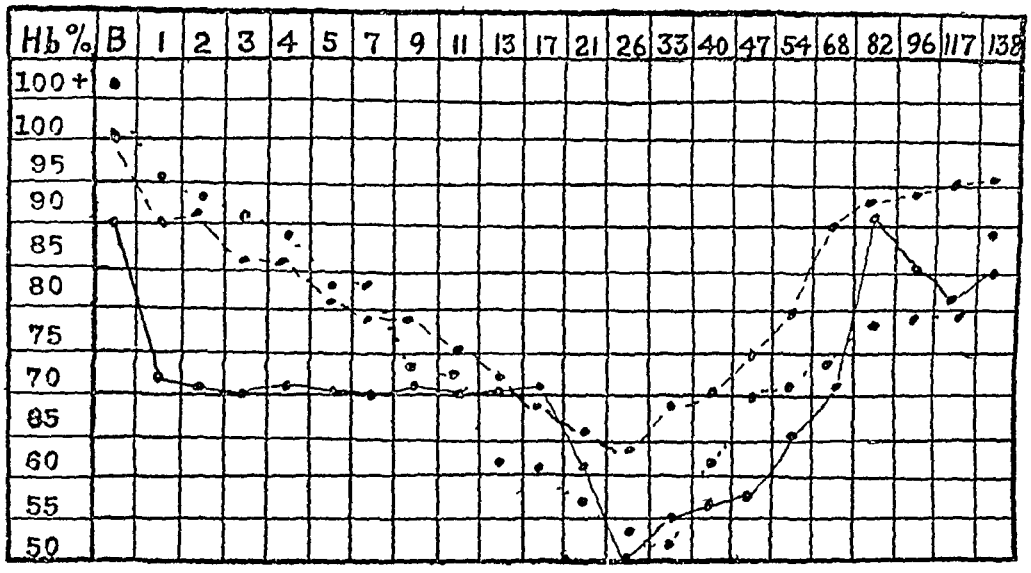

Chart 1.—Showing the effect of splenectomy on the hemoglobin in dogs B = Before operation, upper figures = days after operation, figures to left = percentage of hemoglobin Continuous line = Dog 1, interrupted line = Dog 2, dotted line = Dog 3

Chart 2

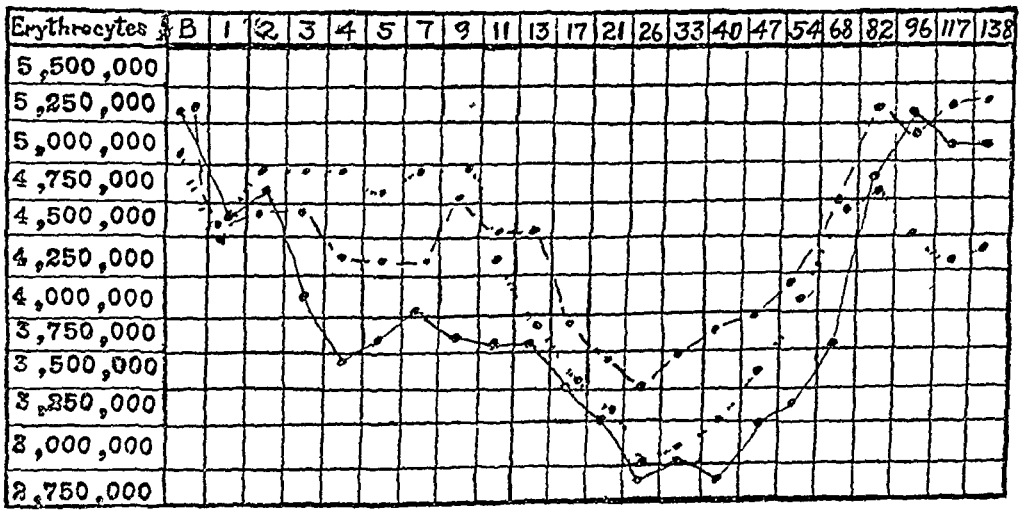

Chart 2.—Showing the effect of splenectomy on the erythrocyte count in dogs Figures to left = erythrocytes per millimeter, B = before operation, upper figures = days after operation Continuous line = Dog 1, interrupted line = Dog 2, dotted line = Dog 3

eosinophils but after the third week no cells of this type were found until the eighty-second day in one dog and the ninety-sixth day in the other two animals The last two counts showed a marked increase in the

number of eosinophils as compared with the counts made before operation Mast cells have only occasionally been seen The number of large mononuclear and transitional forms classified together, also was decidedly lower after the operation and has increased in the last counts, a change comparable to that characterizing the eosinophils Atypical forms of erythrocytes and leukocytes were rare In Dog 1, nucleated red cells were observed five times, the largest number seen in one count being three, none was seen in the other two animals At no time were changes seen in size and general character of the cells, other, of course, than a paler staining, corresponding to a low hemoglobin content Four times in the series of counts basophilic myelocytes were seen, no other atypical leukocytes were observed

SUMMARY

Splenectomy causes in the dog

1 Secondary anemia, lasting about two and a half months

2 A postoperative leukocytosis, most marked twenty-four hours after operation and lasting a variable time, longer indeed than these counts have been carried — 138 days

3 A total absence of eosinophils from about the third to the eleventh week followed by an eosinophilia of a rather pronounced degree

4 A decrease and later an increase in the number of large mononuclears and transitional forms, the lymphocytes and polynuclears being proportionally increased and later decreased

CONCLUSION

On account of the secondary anemia, pronounced at times, and seen both in man and animals, the operation of splenectomy must be considered more seriously than it has been heretofore, at least, measures for the conservation of the general health of the patient and the regeneration of the blood must be kept in mind

TABLE SHOWING EFFECT ON THE BLOOD OF DOGS OF REMOVAL OF THE SPLEEN

DOG 1

Before Op and Days After	Leukocytes	Polynuclears	Lymphocytes	Eosinophils	Other Forms
B *	12,500	138	48	8	6
1	45,200	164	26	2	8
2	24,200	152	34	4	10
3	22,400	154	30	5	11
4	20,400	150	34	8	8
5	21,700	141	30	16	13
7	25,600	146	34	10	10
9	19,700	144	40	2	14
11	21,700	158	26	10	6
13	25 100	156	32	8	4
17	19,700	136	50	8	6
21	18,600	146	48	4	2
26	14,200	128	68	0	4
33	17,100	140	51	0	9
40	16,000	150	47	0	3

TABLE SHOWING EFFECT ON THE BLOOD OF DOGS OF REMOVAL OF THE SPLEEN
DOG 1 (CONTINUED)

Before Op and Days After	Leukocytes	Polynucleais	Lymphocytes	Eosinophils	Other Forms
47	14,500	140	55	0	5
54	10,900	148	44	0	8
68	13,600	146	51	0	3
82	14,700	153	39	2	6
96	13,100	146	36	12	6
111	12,700	126	51	11	12
138	15,900	122	30	26	22
		DOG 2			
B *	10,100	154	32	4	10
1	48,400	181	12	1	6
2	27,900	164	28	4	4
3	25 100	154	30	12	4
4	32,700	158	30	9	3
5	27 400	160	30	3	7
7	23 100	154	50	2	6
9	28,100	165	28	2	5
11	21 500	164	28	4	4
13	18 200	150	40	1	9
17	19,200	158	38	0	4
21	16,800	150	44	0	6
26	14 100	143	50	0	7
33	15,100	148	46	0	6
40	11 600	136	56	0	8
47	12,600	148	43	0	9
54	12 100	147	44	0	9
68	11,400	154	40	0	6
82	12,600	146	45	0	9
96	11 900	140	44	6	10
111	11 800	145	30	13	12
138	16,100	138	22	20	20
		DOG 3			
B *	12,500	138	54	3	5
1	26,900	160	26	8	6
2	25 300	150	38	10	2
3	21,100	150	44	2	4
4	18 600	138	48	6	8
5	13,500	130	58	4	8
7	12,200	144	44	4	8
9	14,800	140	50	4	6
11	13 100	132	60	0	8
13	16,100	140	56	0	4
17	18,800	153	40	0	7
21	14,100	140	51	0	9
26	12,400	133	60	0	7
33	14,100	154	40	0	6
40	14,000	150	43	0	7
47	12 100	142	54	0	4
54	12,100	141	55	0	4
68	12,000	140	56	0	4
82	10 300	144	56	0	6
96	13,100	130	54	7	9
111	13 700	132	52	6	10
138	13,800	140	28	6	26

B = Blood count before operation, numbers below indicate the number of days after operation

THE FREQUENCY OF EXPERIMENTAL GLYCOSURIA FOLLOWING INJECTIONS OF EXTRACTS OF THE HYPOPHYSIS *

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It is generally conceded that patients with acromegaly very frequently show either a transitory or a permanent glycosuria Borchardt,[1] in reviewing the literature of acromegaly, reports that when an examination of the urine is mentioned 35 5 per cent of the cases show a glycosuria and an additional 5 per cent a lessened sugar tolerance Inasmuch as the glycosuria is often transitory and not infrequently independent of the character of the diet, unless the urine is repeatedly examined it may be overlooked The presence of the glycosuria might be accounted for either on the one hand by pressure of the enlarged anterior lobe on the hypothetical sugar center or on the adjacent posterior lobe of the hypophysis, or on the other by the action of the hypophyseal secretion on sugar metabolism, either directly or through its correlated action with the thyroid or suprarenals It has been noted that tumors of the hypophysis not associated with acromegaly are not apt to be accompanied by a glycosuria Tumors about the infundibulum, especially those developing from mouth epithelium, are frequently accompanied by polyuria without glycosuria It has been suggested that the glycosuria might possibly be due to the pressure of the enlarged anterior lobe on the posterior lobe of the hypophysis There is no experimental or clinical evidence, however, to show that glycosuria can be due to lessened functioning of the posterior lobe As a rule in acromegaly there is an adenomatous hyperplasia of the anterior lobe, or, in cases in which it is not enlarged, an increase in its specific secretory cells It is, therefore, generally believed that acromegaly is due to hypersecretion of the anterior lobe of the hypophysis

If the secretion of the hypophysis was directly responsible for the appearance of sugar, it might be expected that extracts of the gland when administered to an animal would excite a glycosuria With this in mind several investigators have undertaken the experiment with varied results

Borchardt,[1] injecting rabbits subcutaneously, obtained positive results in twenty-eight out of thirty-five animals The amount of sugar varied from a trace to 4 27 per cent It usually appeared within two or three

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*From the Laboratory of Experimental Therapeutics, University of Chicago

1 Borchardt, L Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, Ztschr f klin Med, 1908, lxvii, 333

hours after the injection and rarely persisted for more than twenty-four hours In the seven negative tests even very large amounts of the extract failed to produce a glycosuria He also tried the same experiment on seven dogs Five developed a transitory glycosuria, but in none of them could the results be considered conclusive, as the conditions present were abnormal Two of the dogs showed a glycosuria only when fed on a large amount of carbohydrates, and in one of these the sugar first appeared twenty-four hours after the injection From two of the animals in which a spontaneous glycosuria developed when fed on carbohydrates but which remained sugar-free on a meat diet, a large portion of the pancreas had previously been removed These two animals, when fed on meat, developed a glycosuria after the subcutaneous injection of the hypophyseal extract Finally, the other positive dog had an intense tremor following the injection, a not unusual experience after injections of the hypophyseal extracts, especially of the posterior lobe This tremor, by shaking the glycogen from the muscles, might account for the glycosuria Bossi reported a glycosuria in dogs after subcutaneous injections, but his results are questionable, as he employed 0 5 per cent phenol (carbolic acid) as a preservative, sufficient in itself, as shown by Bukowski, to produce a glycosuria Pal obtained negative results Franchini[2] injected twenty-two rabbits with extracts, either of the entire hypophysis or of the separate lobes, he employed both subcutaneous and intravenous administration and obtained positive results in only two animals, and then only shortly before death As both of these animals showed extensive lesions of the intestine, Franchini considers this the cause of the glycosuria As Gaultier, Minkowski and others have shown, irritation or mechanical injury to the bowel may give rise to glycosuria

With these conflicting results, it was thought that it might be of interest to repeat these experiments, using extracts from the separate lobes Small dogs were selected, rather than rabbits The well-known tendency of the rabbits to spontaneous glycosuria, and the readiness with which it can be excited by indifferent agents, render these animals unsuitable for this particular work Only those cases were recorded in which the uncontaminated urine was obtained This was at times difficult on account of the gastro-intestinal disturbances excited by the injection

Fresh ox hypophyses were obtained at the stock yards The two lobes were separated, cut into small pieces, dried and powdered and from this a normal salt extract was prepared Some of the animals received the solution intravenously, others intraperitoneally The latter method was used, as Herter and Wakeman reported the most marked suprarenal glycosuria after intraperitoneal injections In the examination for sugar

2 Franchini, G Die Funktion Hypophyse und die Wirkungen der Injektion ihres Extraktes bei Tieren, Berl klin Wchnschr, 1910, xlvii, 613

the urine was first tested with Fehling's solution, if reduction occurred the polariscope and fermentative tests were tried This is essential as the dog's urine very frequently contains a reducing substance which is not sugar

In all, thirty animals were injected, fifteen with extracts of the anterior lobe and the same number with extracts of the posterior lobe Several urines contained a reducing substance, but only three proved to contain sugar Two of these animals had received injections of the dried preparation of the entire anterior lobe, 0 4 and 2 gm One had received an injection of 12 c c of pituitrin, an extract prepared from the posterior lobe All three of the positive animals had received intraperitoneal injections The percentage of sugar as determined by the polariscope was 0 48 per cent and 0 5 per cent from the anterior lobe, and 0 75 per cent from the posterior lobe The glycosuria was always transitory, disappearing within twenty-four hours No special polyuria was noted in these three cases, although it was frequently observed after injections of the posterior lobe, or after injection of a portion of the anterior lobe adjacent to the cleft, which, histologically, is pars intermedia Extracts of the anterior lobe distant from the cleft did not excite diuresis

If we are justified in drawing any conclusions from the above results, as to the effects of the extracts of the hypophysis in producing glycosuria, it must be that the substance responsible is present in both lobes As the pars intermedia is common to both the anterior lobe and the posterior lobe of the hypophysis, it might be assumed that this portion was responsible for the glycosuria It is a question, however, in these three animals, whether the glycosuria was the result of disturbed sugar metabolism due to the specific action of the hypophyseal extract or to other factors As a rule, following either intravenous or intraperitoneal injection of extracts from the anterior or posterior lobes certain symptoms are noted The most striking of these are gastro-intestinal disturbances, dyspnea, tremor and finally extreme lassitude The gastro-intestinal disturbances are unusually severe with vomiting, purging and often within a few minutes stools containing mucus and blood Franchini[2] has already called attention to the intestinal lesions following the use of hypophyseal extracts, and also to the rôle such lesions may exert in exciting a glycosuria Respiratory disturbances are a well-recognized cause of glycosuria Underhill[3] and others have shown that in the presence of dyspnea there is hyperglycemia and glycosuria The glycosuria following nicotin and pyridin is probably due to the action of these drugs on the respiratory center Henderson reports glycosuria after injecting peptones, owing, as he believes, to the acapnia arising from accelerated respiration Almost con-

3 Underhill, F P Certain Aspects of Experimental Diabetes, Jour Biol Chem, 1905, 1, 113

stantly after injecting extracts of the hypophysis there is labored breathing, probably identical with that following peptone injection, and this might readily account for the glycosuria Finally, it has been shown that after prolonged severe tremor, sugar may appear in the urine The tremor following the injection of hypophyseal extracts may be severe and prolonged

It is not improbable that one or all of the above factors may be responsible for the glycosuria rather than any specific action of the hypophyseal extract This explanation appears the more probable on account of the infrequent occurrence of the glycosuria, which we would not expect if it were specific in character

Glycosuria has frequently been reported in dogs after partial removal of the hypophysis Goetsch, Cushing and Jacobson[4] found a glycosuria after operative manipulation of the hypophysis, due, they believe, to the setting free of an excessive amount of the secretion of the posterior lobe On account of the readiness with which glycosuria may be excited by anesthesia, great care must be exercised in drawing conclusions as to the exact nature of the glycosuria following operative procedures We attempted to determine whether painting the pancreas with extract of the hypophysis would produce a glycosuria, as Harter and Wakeman had done with suprarenal extract It was found, however, after the dog had been etherized for an hour, that spontaneous glycosuria developed In our experiments, the development of a glycosuria after ether anesthesia was not an exceptional but a uniform occurrence In one instance, the amount of sugar was 6 2 per cent Hawk[5] has recently shown that anesthesia of twenty minutes' duration may excite a glycosuria in dogs

CONCLUSIONS

Intravenous or intraperitoneal injections of saline extracts of either the anterior or posterior lobe of the hypophysis will occasionally produce a transitory glycosuria in dogs It is doubtful whether or not this is due to the specific action of the extract on sugar metabolism The tremor, marked respiratory symptoms, and intestinal disturbance following the injection are sufficient to account for it

4 Goetsch, E, Cushing, H, and Jacobson, C Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, Bull Johns Hopkins Hosp, 1911, xxii, 165

5 Hawk, P B Postanesthetic Glycosuria, THE ARCHIVES INT MED 1911, viii, 39

THE OCCURRENCE OF NATIVE ANTISHEEP AMBOCEPTOR IN HUMAN SERUM AND ITS IMPORTANCE IN THE PERFORMANCE OF THE WASSERMANN REACTION *

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That there occurs in certain human serums a substance which hemolyzes sheep corpuscles in the presence of complement has been known for a considerable time It has been our purpose to find out how much the presence of this substance in serums which reacted positively to the Wassermann test could affect the final result of the reaction

In 1908 Bauer[1] pointed out that use might be made of this substance — to which we shall refer as native antisheep amboceptor — in the complement fixation test for syphilis, and he suggested substituting this native amboceptor for the rabbit sheep amboceptor used in the Wassermann reaction The Wassermann technic would be simplified in this way, as one of the reagents would be eliminated without endangering its accuracy This procedure is known as the Bauer modification of the Wassermann reaction Shortly after this, Bering[2] reported a series of 123 cases, in which both the Wassermann reaction and the Bauer modification were used He found that the results of the two reactions checked in all of the 123 cases, but other observers who compared the two methods found that the presence of this native antisheep amboceptor was too inconstant to be depended on Hoehne[3] found that at least 10 per cent of the adults had in their serum either none of this substance or an insufficient amount for the reaction Meirowsky[4] found Bauer's modification to be inaccurate and unreliable as compared with the Wassermann reaction Swift[5] compared the results of the Bauer reaction with the Wassermann and Noguchi reactions in sixty-five serums He found sufficient native amboceptor to carry out the Bauer modification in 38 per cent of the cases, and an insufficient amount in 60 per cent of the cases Noguchi[6] found that this native antisheep amboceptor varied much in different

*From the H K Cushing Laboratory of Experimental Medicine, Western Reserve University, Cleveland Received for publication Feb 5

1 Bauer, J Deutsch med Wchnschr, 1908, xxxiv, 698, Berl klin Wchnschr, 1908, xlv, 834

2 Bering, F Munchen med Wchnschr, 1908 xlviii, 2476

3 Hoehne, F Berlin klin Wchnschr, 1910, xlvii, 334

4 Meirowsky, E Berl klin Wchnschr, 1909, xlvi, 152

5 Swift, H F THE ARCHIVES INT MED, 1909, iv, 376

6 Noguchi, H Jour Exper Med, 1909, ix, 392

serums, in some instances the amboceptor content was as high as 20 units Kalıskı[7] found from slight to large amounts in about 53 per cent of human adults The above observations go to show that while there is in certain human serums enough antisheep amboceptor to hemolyze the amount of sheep cells used in the Wassermann reaction, this is by no means a constant characteristic

Morgenroth and Sachs,[8] Noguchi[9] and others have shown that with a constant amount of red cells, hemolysis will occur when the amounts of amboceptor and complement are varied inversely to each other In other words, hemolysis will occur with a constant amount of sheep corpuscles even if less than one unit of complement be used when the amount of amboceptor is increased proportionately It is therefore conceivable that in a serum which contains enough native amboceptor for the purposes of a complement fixation test, the addition of the usual dose of artificial amboceptor might well change a positive reaction into a negative one by causing hemolysis to take place where none should occur

In order to obtain an idea of the amount of native antisheep amboceptor in human serums which were to be tested by the Wassermann reaction, Swift[5] suggested the addition of a new control tube to the Wassermann system This tube would contain one-half the amount of human serum used in the test, with the usual amount of complement and sheep-cell emulsion He thought that if hemolysis occurred in this control tube "it would give a clue to the cause of negative findings with certain serums and would justify repeating the reaction with the Bauer modification"

Acting on this suggestion we have controlled a large number of Wassermann reactions with this extra test We have used the modified Wassermann system recommended by Swift,[5] in which one-half the amount of serum and reagents employed in Wassermann's original technic are used The tube containing only the patient's serum, complement and cell emulsion, which we may call the Bauer control tube, is incubated for one hour, during which time the reactions undergo their first incubation If at the end of the hour the Bauer control shows complete hemolysis it has been our custom to perform the test without the addition of the artificial amboceptor, depending on the native amboceptor to carry out the reaction

We have controlled 1,686 reactions in the above manner and have found sufficient native amboceptor in 301 serums (17 9 per cent), while in 1,385 (82 1 per cent) there was either none or an insufficient amount

We have also reviewed our notes on ninety-five additional cases in which two or more Wassermann reactions had been done In sixty-two

7 Kalıskı, D J THE ARCHIVES INT MED, 1910, vi, 205
8 Morgenroth, J, and Sachs, H Berl klin Wchnschr, 1902, xxxix, 817
9 Noguchi H The Serum Diagnosis of Syphilis, J B Lippincott Co, 1910

of these cases there was no native antisheep amboceptor at any time Five showed a sufficient amount of native amboceptor constantly on two or more observations, while twenty-eight cases showed an insufficient amount of native amboceptor on one occasion and a sufficient amount on others, or vice versa These observations were made over periods of time varying from weeks to months, and merely suggest that the native antisheep amboceptor in human serum is a distinctly inconstant body even in one and the same individual

TABLE OF POSITIVE REACTIONS CHANGED BY THE ADDITION OF ARTIFICIAL AMBOCEPTOR*

No	Without Artificial Amboceptor	With Artificial Amboceptor	No	Without Artificial Amboceptor	With Artificial Amboceptor
1	+++	++	15	+++	—
2	+++	++	16	+++	—
3	+++	++	17	++	+
4	+++	++	18	++	+
5	+++	++	19	++	±
6	+++	++	20	++	±
7	+++	++	21	++	—
8	+++	+	22	++	—
9	+++	+	23	+	±
10	+++	+	24	+	±
11	+++	±	25	+	—
12	+++	±	26	+	—
13	+++	±	27	+	—
14	+++	±	28	+	—

*In this table +++ means strongly positive (no hemolysis), ++, positive (distinct hemolysis without visible diminution in the layer of cells at bottom of tube), +, feebly positive (hemolysis with some diminution in the layer of cells at bottom of tube), ±, plus-minus (marked hemolysis with only a faint layer of cells at bottom of tube), —, negative (complete hemolysis)

As already stated, the main purpose of the observations discussed in this paper was to find out how far positive Wassermann reactions in serums which showed a sufficient native antisheep amboceptor content could be affected by the addition of the usual dose of artificial amboceptor In the series specially devoted to this purpose, our procedure has been to perform two separate reactions on such serums One reaction was carried through without the addition of artificial amboceptor, i e, with the Bauer modification, while the second reaction received the usual dose of artificial amboceptor We have done a large number of reactions in this manner, of which seventy-seven serums showed a positive reaction to the Bauer modification

Of these seventy-seven positive reactions forty-nine, or 63 6 per cent, remained unchanged by the addition of artificial amboceptor, while twenty-eight, or 36 4 per cent, were changed by the addition of artificial amboceptor

Of the forty-nine reactions which were unchanged, forty-one were strongly positive (+ + +), four were positive (+ +) and four were feebly positive (+)

Of the twenty-eight reactions altered by the addition of artificial amboceptor, sixteen were classed as strongly positive Of these sixteen reactions seven were changed to positive (+ +), three were changed to feebly positive (+), four were changed to plus-minus reactions (±) and two became negative (—) (see table)

There were six reactions classed as positive Of these two were changed to feebly positive reactions (+), two were changed to plus-minus reactions (±) and two became negative

There were six reactions classed as feebly positive Of these two became plus-minus reactions, and four became negative

Further, there were eight reactions not counted in the above series, classed as plus-minus reactions, all of which became negative

CONCLUSIONS

Of the twenty-eight positive reactions which were altered by the addition of artificial amboceptor, eight were changed to frankly negative reactions and eight became plus-minus reactions, which could not be considered positive Thus it is interesting to note that out of the seventy-seven serums observed, there were sixteen positive reactions (21 8 per cent) which became either entirely negative or ambiguous and for practical purposes could only be considered negative

It seems justifiable to conclude that while the presence of a native antisheep amboceptor in human serum is by no means constant it is essential to take note of its presence or absence in performing the complement fixation test for syphilis by the Wassermann method, and that if this precaution be not taken, a certain and by no means very small percentage of positive reactions will be recorded as negative By following this simple method of controlling the reaction this error will be obviated to a large degree

The Rose Building

STUDIES OF THE LEUKOCYTES IN PULMONARY TUBERCULOSIS AND PNEUMONIA*

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It has long been recognized that the leukocytes of the circulating blood play an important rôle in many, if not all, bacterial infections, and numerous investigations have already contributed valuable additions to our knowledge of this subject

The researches of Arneth, calling attention to the morphology of the nucleus in the neutrophil leukocytes, especially in tuberculosis, have stimulated further studies in this direction on the part of various observers The results reported in this paper were first suggested by the work of Arneth and represent an effort to corroborate and amplify his results by various experimental and clinical observations and especially to determine their value in the diagnosis and prognosis of pulmonary tuberculosis and pneumonia

It seemed possible that Arneth had laid undue emphasis on the significance of the neutrophil leukocytes and that it was important to study the other forms of leukocytes in connection with them Pneumonia was chosen as a companion study with pulmonary tuberculosis, as forming a contrast of an acute with a chronic pulmonary disease.

An effort has been made to collect the information which is widely distributed in the literature, and by correlating our own results with that of others, to try to present a fairly complete study of the behavior of the white blood-cells in these two diseases

The clinical material was obtained from the tuberculosis clinic, day camp and wards of Bellevue Hospital, and in the case of pneumonia from the medical wards of Bellevue Hospital, many of the cases observed being under the services of Dr George R Lockwood and Dr William K Draper, to both of whom we are deeply indebted for the privilege of studying these cases

THE LEUKOCYTES IN NORMAL INDIVIDUALS

As a basis of such a study, it is essential to establish the normal conditions both as to total number of leukocytes in the blood and as to their distribution among the various classes as shown by the differential count

* Read before the American Climatological Association in Montreal, Can, June, 1911, received for publication Dec 1, 1911

Almost all authorities place the normal number from 5,000 to 10,000 per cubic millimeter The text-books have evidently appropriated these results from the earlier observations of Hayem,[1] Turk,[2] Grawitz,[3] Naegeli[4] and others A recent careful study by Kjer-Petersen,[5] however, places the average normal number between 4,000 and 5,000 in men and comes to the conclusion that in women the normal count is very irregular, varying from 4,000 to 25,000 under various physiological conditions

This observer lays great stress on the fact that the blood is often not homogeneous, this being especially apt to be the case in women He attributes the higher counts usually noted to improper methods, laying particular stress on the necessity of taking the specimen of blood when the subject is fasting before breakfast and also on the importance of invariable close approximation of the cover-slip to the counting chamber so as to produce Newton's rings Arneth, Steffen and others agree with Kjer-Petersen In our own studies we found the average number of leukocytes in a large number of counts to be 9,000

In the normal differential count there is considerable variation among the various authorities This is largely due, however, to the fact that there is no unanimity of opinion as to what types of cells are included in the various groups Table 1 gives the figures quoted by several independent observers

TABLE 1.—NORMAL DIFFERENTIAL COUNT

	Polynucleais	Transitionals	Large Mononuclears	Large Lymphocytes	Small Lymphocytes	Eosinophils	Basophils
Cabot[6]	62-70			4-8	20 30	0 5-4	1/45-0 9
Ewing[7]	70-72	2	4	22	25	2-4	0 5-2
Wood[8]	65-75	2 4	1	22	25	2-4	0 5
Naegeli[4]	65-70	3	5	22	25	2 4	0 5
Webb and Williams[9]	54			24	19	2	0 4
Da Costa[10]	60 75	4	8		20-30	0 5 5	0 5

Many emphasize the importance of calculating the actual number of each class of cells rather than indicating the results by percentages In our work we have discarded the terms "transitional" and "large mono-

1 Hayem Le sang et ses alterations anatomiques, Paris, 1899, G Masson
2 Turk Verhalten des Blutes bei akuten Infektionskrankheiten, Vienna, 1898, W Braumuller
3 Grawitz Hæmatologie, Leipsic, 1907, G Thieme, Klinische Pathologie des Blutes, Berlin, 1902, O Enslin, Berl klin Wchnschr, 1894, xxxi 100
4 Naegeli Blutkrankheiten und Blutdiagnostik, Leipsic, 1907, Veit and Co
5 Kjer-Petersen Beitr z Klin d Tuberk, 1906, Supp -Vol 1
6 Cabot Clinical Examination of the Blood, New York, 1904, William Wood and Co
7 Ewing Clinical Pathology of the Blood, New York and Phila, 1903, Lea Brothers and Co
8 Wood Chemical and Microscopical Diagnosis, New York, 1909, D Appleton and Co
9 Webb and Williams Tr Nat Assn Prev Tub, 1909, v, 231
10 Da Costa Clinical Hematology, Phila, 1905, P Blakiston's Son and Co

nuclear," and in our differential count these cells, as described by others, are probably partly included in the polynucleais and partly in the large lymphocytes

THE BIOLOGY OF THE LEUKOCYTES

In order to understand properly the significance of the differential count of the leukocytes, particularly the work of Arneth,[11] it is valuable to summarize briefly the theories concerning the development of the leukocyte

There are two general theories regarding this development, dividing hematologists into two distinct schools One, under the leadership of Ehrlich,[12] considers that the polynuclear neutrophils, eosinophils and basophils are derived only from their corresponding marrow-cells and that there is never a transition from the lymphocytes to the polynuclear forms The lymphocyte, according to this school, develops from the various lymphoid organs, some even from lymphoid tissue in the marrow and pass through the various stages of lymphoblasts, large lymphocytes and small lymphocytes, but never into the types of cells with granular cell bodies

The large mononucleais and transitional cells, according to this school, are separate entities derived from the marrow and the transitional cells probably are derived from large mononucleais and in turn are trans-

11 Arneth Die neutrophilen weissen Blutkorperchen bei Infektionskrankheiten, Jena, 1904, G Fischer, Zum Verhalten der neutrophilen Leukozyten bei Infektionskrankheiten, Munchen med Wchnschr, 1904, li, 1097, Die agonale Leukozytose, Munchen med Wchnschr, 1904, li, 1195, Experimentelle Untersuchungen zum Verhalten der weissen (und roten) Blutkorperchen bei Infektions und Intoxikationsversuchen, sowie nach Einverleibung von Eiweisskorpern und Heilserris, Ztschr f klin Med, 1905, lvii, 288, Munchen med Wchnschr, 1904, li, 1993, Die kachektische Leukozytose, Verhalten der neutrophilen Leukozyten beim Carcinom, Ztschr f klin Med, 1904, liv, 238, Blutuntersuchungen bei der Tuberkulose der Lungen und bei der Tuberkulinkur, Munchen med Wchnschr, 1905, lii, 542, Die Lungenschwindsucht auf Grundlage klinischer und experimenteller hæmatologischer Untersuchungen, Ztschr f Tub, 1905, vii, 309, 405, Erwiderung zu Hiller's Beitrage zur Morphologie der neutrophilen Leukozyten und ihrer klinischen Bedeutung, Folia Hæmatologica, 1905, ii, 169, Zu meinen Blutuntersuchung (Nachprufungen, einige weitere Beitrage), Erwiderung zu Flesch und Schossberger, Deutsch Arch f klin Med, 1906, lxxxvii, 209, H Pollitzer's Anschauungen, uber die Kernbeschaffenheit der neutrophilen Leukozyten unter normalen und pathologischen Verhaltnisse, Wien med Wchnschr, 1907, lvii, 430, Entgegnung zu H Pollitzer's zu Arneth's Verschiedung, etc, Deutsch Arch f klin Med, 1908, xciv, 217, Zu H Pollitzer's Beitrage zur Morphologie und Biologie, etc, Folia Hæmatologica, 1908, vi, 210, Zu Paulicek Zur qualitativen Blutuntersuchung nach der von Arneth angegebenen Methode, Folia Hæmatologica, Supplement, 1907, 167, Entgegnung zu Bourmoff und Brugsch Das neutrophile Blutbild bei Infektionskrankheiten, Ztschr f klin Med, 1907, lxiv, 170, Das Neutrophile Blutbild bei Infektionskrankheiten Gegenerwiderung zur Antwort van T Brugsch, etc, Ztschr f klin Med, 1908, lvi, 192, Diagnose und Therapie der Anaemien, Wurzburg, 1907, A Stuber Die Leukozytose in der Schwangerschaft, etc, und die Leukozytose der Neugeborenen, Arch f Gynakol, 1904, lxxiv, 145

12 Ehrlich Farbenanalytische Untersuchungen z Histologie u Klinik des Blutes, Berlin, 1891, A Hirschwald

formed into neutrophils Pappenheim,[13] Naegeli,[4] Weidenreich[14] and the majority of observers now accept this theory

The other theory, which is held by the Russian school under the leadership of Uskow, and which is also supported by Grawitz, holds that the neutrophil cells are frequently derived from the lymphocytes, and that the so-called transitionals often represent a stage between these two types of cells

Practically all authorities agree that the true lymphocytes do not act as phagocytes, although it has been demonstrated that they do in some way hinder the development of the bacterial infection in the body

In the development of the neutrophils, Arneth's contention is that their progress from the myelocyte is marked by changes in the nucleus, it being first indented and bent and finally lobulated, the mononuclear forms, therefore, representing the younger and the multimononuclear forms the older type of cells The granules also are more numerous in the older cells In the younger cells the granules are apt to be first basophilic and later oxyphilic The origin and significance of the eosinophils have been carefully studied by Brown, but accurate scientific knowledge of them is still lacking

ARNETH'S BLOOD-PICTURE

In developing his theory of the changes of the nucleus during the growth of the neutrophil, Arneth has divided the neutrophils into various classes according to the number and shape of the nuclear segments This he tabulates into a very involved blood-picture His contention, supported by numerous clinical observations is that in various diseases the differential count of the neutrophils, according to his scheme, very often shows an abnormal predominance of the younger forms of cells, which he calls a shifting to the left in his blood-picture, that this shifting is very characteristic and represents a definite reaction on the part of the organism to the infection, and that a study of these changes forms a valuable basis for the differentiation of diseases and knowledge of their clinical course and subsequent history

Arneth's work has attracted a good deal of attention and many reports based on his theory have appeared in the literature Hiller,[15] in addition to finding Arneth's method unreliable clinically because of the great variations in the normal, and because of the fact that the changes noted bore no relation to the severity of the disease, disagrees with the theory of Arneth, contending that the neutrophils are derived from lymphocytes Pappenheim[13] successfully refutes his contentions Pollitzer[16] dissents

13 Pappenheim Folia Hæmatologica, 1905, 166, Atlas d menschliche Blutzellen, Jena, 1905, G Fischer

14 Weidenreich Arch f microsc Anat 1908, lxxii, 209

15 Hiller Folia Hæmatologica, 1905, 85

16 Pollitzer Wien med Wchnschr 1906, lvi, 862, Deutsch Arch f klin Med, 1907, xcii, 1, Ztschr f Heilk, 1907, Section f Path Anat, viii, 239

very strongly from Arneth as to his theory of development of the nucleus, and also holds that the changes in the nucleus noted are due to artefacts caused by the method of staining

Arneth's reply to our own investigations discredits Pollitzer's contentions Busse[17] objects on the ground that experiments showed that there was no variation of phagocytic power among the different classes of neutrophils according to the number of nuclear segments He consequently argues against Arneth's conclusions that these variations in the nucleus denote variations in efficiency against infection. Arneth, in his reply, denies the importance of these observations

Zangemeister and Ganz[18] object to Arneth's method of considering the neutrophils to the exclusion of the other forms of leukocytes and also to Arneth's classification Their experiments with streptococci tend to show that the mononuclear neutrophils are the most important from the standpoint of prognosis, the polynuclear neutrophils and the eosinophils coming next in order

Flesch and Schossberger[19] studied many diseases in children, and while agreeing to the fact that the shifting to the left did occur under various conditions, found that this shift had no relation to the clinical course of the disease Pollicek[20] also found that in tuberculosis the blood-picture was of no value clinically either in diagnosis or prognosis Bourmoff and Brugsch[21] came to similar conclusions In this country Kagan[22] and Solis Cohen and Strickler[23] found Arneth's method of no clinical value

Many other observers, however, particularly recently, have corroborated Arneth Among these are Bochenski,[24] Kownatski[25] and Grafenberg[26] in sepsis, particularly in puerperal fever, Kohl[27] and Kothe[28] in appendicitis, Sonnenberg and Kothe[29] in peritonitis, Esser[30] in intestinal diseases of children and Lewinson in several diseases, found Arneth's method of value both in diagnosis and prognosis Many others have corroborated Arneth's methods in tuberculosis These will be noted more in detail later

17 Busse Munchen med Wchnschr, 1910, lvii, 70
18 Zangemeister and Ganz Munchen med Wchnschr, 1909, lvi, 793
19 Flesch and Schossberger Jahrb f Kinderheilk, 1905, lxii, 249
20 Paulicek Folia Hæmatologica, 1907, iv, 751
21 Bourmoff and Brugsch Ztschr f klin Med, 1907, lxiii, 489
22 Kagan Boston Med and Surg Jour, 1910, clxii, 709
23 Solis Cohen and Strickler New York Med Jour, 1910, xcii, 248
24 Bochenski Gynakol Rundschau, 1909, iii, 148
25 Kownatzki Beitr z Geburtsh u Gynakol, 1906, x, 275
26 Grafenberg Arch f Gynakol, 1908, lxxxv, 302
27 Kohl Mitt a d Grenzgeb d Med u Chir, 1911, xxii, 542
28 Kothe Berl klin Wchnschr, 1908, xlv, 1633, Munchen med Wchnschr, 1909, lvi, 1130
29 Sonnenberg and Kothe Deutsch Ztschr f Chir, 1909 c, 101
30 Esser München med Wchnschr, 1906, liii, 1651

BLOOD-PICTURE INDICES

Many observers, including ourselves, have found Arneth's method very cumbersome on account of the multiplicity of detail and on account of its consequent lack of definiteness, which impairs its clinical value Various suggestions have been made by which the variations in the nucleus of the neutrophils might be noted by a definite index For this purpose some use as an index simply the number of the neutrophils which are mononuclear, claiming this as a sufficient measure of the shifting to the left These observers are Zangemeister and Ganz[18] Kothe,[28] Sonnenberg and Kothe[29] and Kohl[27] Others, including Klebs,[31] Dluski and Rospedzihowski[32] and Minor and Ringer,[33] use the sum of Classes 1 and 2 of Arneth's picture as an index

Adolph Wolf[34] advocates a total nuclear count of the neutrophils, counting the round segments as one and the bent or loop forms as one and one-half, and in counting he notes only the number of these two types of nuclei and totals them for his nuclear counts Von Bonsdorff[35] has a similar method somewhat modified Sabrazès[36] has worked out a neutroleukocytic and neutro-nucleo-leukocytic quotient as an index Bushnell and Treuholtz[37] use the sum of Classes 1 and 2 and one-half of Class 3 as an index In our observations we have followed this suggestion as it seems to lose less of the value of Arneth's original classification than do the others

TECHNIC

In our observations the specimens of blood are usually, but not invariably, obtained in the afternoon from three to four hours after the ingestion of food The other more usual causes of physiological leukocytosis, such as exercise and cold baths, were avoided Also, no cases were studied after hemorrhage

We emphasize, as have others, the importance of obtaining thin and even smears of the blood for differential count and of close approximation of the cover slips to the counting chamber for enumeration

After numerous experiments in various methods of fixing and staining we found that fixing by drying in the air and passing the slide two or three times across the flame, and the use of Wright's stain made up fresh produced the best results for the study of the nuclei Enough stain is dropped on the slide to cover the smear, and the dish then covered for one minute It is most important to have fresh stain often, as Wright's stain does not keep well

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31 Klebs Am Jour Med Sc, 1906, cxxxii, 538
32 Dluski and Rospedzihowski Beitr z klin d Tuberk, 1909, xiv, 259
33 Minor and Ringer Am Jour Med Sc, 1911, cxli, 638
34 Adolph-Wolff Die Kernzahl der Neutrophilen, Heidelberg, 1906
35 Von Bonsdorff Folia Hæmatologica, 1910, ix 242
36 Sabrazès Arch d mal d cœur, d vaisseaux et du sang, 1910, iii, 484
37 Bushnell and Treuholtz Med Rec, 1908, lxxiii, 471

The slide is left for two or three minutes with the stain, at the end of which time eight or ten drops of tap water are dropped on and the dish again covered for one minute or until the metallic scum appears, when the slide is washed by dipping into a glass of distilled water and out quickly, when it is blotted and dried All counts should be made with the oil immersion lens

One hundred neutrophil cells were counted in each observation and the other forms of cells found during this count were noted, so that an average of 140 to 150 leukocytes were counted in each observation

Many slides were studied by two or three separate observers, and the similarity of the results in the Arneth counting satisfied us that it is an accurate clinical procedure

In differentiating segments of the nuclei, superimposed segments were always counted separately, as also were those connected by thread Those having a connecting isthmus, however, were counted as one segment

EXPERIMENTAL WORK

Many experiments were carried out to aid in as complete an understanding of the changes found in the white blood-cells as possible, especially in relation to Arneth's studies with the neutrophils

These experiments can be summarized under the following headings

1 Staining Experiments These were undertaken to determine which stain would give the best nuclear picture, and at the same time to differentiate the different classes of leukocytes in the blood

Smears were prepared in the usual manner except that the slides were clean and as sterile as possible and the blood was spread in a thin and even film The smears were killed in all the well-known cytological methods and each method of killing and fixing was stained by the three usual differential blood-stains, that is, Wright's differential, Jenner's differential and the eosin and methyl blue method Many other slides were stained with iron hematoxylin, Ehrlich's triacid stain, and with Goldsmith's triple stain

The results from these experiments showed that the best method for preparing the slides was to kill the blood-smear by simple drying and to fix and stain with Wright's differential stain, which gave the best nuclear picture as well as differentiated the leukocytes Jenner's stain does not give a good nuclear stain and fades rapidly, so it was not used

For the cytological study of the nucleus, slides killed with hot corrosive sublimate and stained with iron hematoxylin gave the best picture The usual method for the study of the nucleus, i e , to kill with Flemming strong and stain with iron hematoxylin did not give satisfactory results with the blood-smears

2 The Question of Artefacts These experiments were suggested by Pollitzer's article,[16] in which an attempt is made to prove that the number of pieces of lobes found in the nucleus of the neutrophils is an artefact and has no connection with the state of the nucleus in the living neutrophil

(*a*) Smears were prepared from the blood of three subjects, each of which showed an Arneth index slightly different from the other These smears were prepared in all the known cytological methods and numbered with a key so that at the time they were counted it was not known from which subject the slide had been prepared It was found that the smear from each subject gave practically the same index, even where the preparation had been so poor as to be almost useless and that the difference between the indices of the blood-pictures from the three subjects remained the same as in the smears prepared by Wright's differential method

(*b*) Smears were prepared in which an attempt was made to stretch and tear the nucleus in order to discover whether there were more or fewer number of lobes to the nucleus than was shown by Wright's differential method Slides were scratched with emery paper and then cleaned and the blood drawn slowly across the scratches so as to catch and tear the neutrophils

Counts made from such preparations gave the same neutrophilic blood-picture as did the smears prepared by the normal Wright's differential method In some cases the neutrophil was stretched to several times its normal length, but in all such cases the nucleus stretched also and the number of lobes remained the same

These experiments demonstrate that the number of lobes of the nucleus is not an artifact due to any *one* stain, but is a definite state taken by the nucleus when killed, which must indicate some definite differences in the state of the nucleus of the different living neutrophils

3 Normal Blood-Picture in Man and in Guinea-Pigs (*a*) Smears were prepared from over twenty different persons whose condition was, as far as known, normal These different blood-pictures gave indices which varied slightly from each other and yet varied within a small range, which could be called normal This blood-picture corresponded very nearly with that of Arneth, which was taken from a large number of subjects

(*b*) Smears were obtained from a few subjects at different times of day for a period of time extending over a week or several weeks and in two cases extending over a period of two years The results in these cases show indices which vary, but not definitely enough to be attributed to any one cause, and the amount of the index variation in each case was so slight as still to come within the limits of the normal blood-picture, except in the case of one of the subjects studied for a period of two years, in which the blood-picture shifted decidedly, owing to appendicitis

These observations showed that the average normal blood-picture was· I/5, II/26, III/36, IV/28, V/5 leukocytes, 9,000, index, 49 51, but that any blood-picture with an index between 45 55 and 55 45 may be called normal unless one of the classes should be in some way most unusual

(*c*) Ten guinea-pigs were studied for a period of over two weeks Smears were prepared from the blood of these animals every two hours during the day The result gave a picture comparable to that of the human blood, except that the number of the lobes of the nucleus of the neutrophil is greater in the guinea-pig than in man, and the index is therefore different The normal guinea-pig neutrophilic blood-picture is as follows I/5, II/20, III/38, IV/30, V/6, VI/5 leukocytes, 10,000, index, 42 58

The blood-picture as shown by the guinea-pig varies more for the individual animal than it did for the individual person, so that in all experiments with guinea-pigs, the animals were kept for a week or ten days and the normal blood-picture established for each animal before the experiment was begun.

4 Effect on Neutrophilic Blood-Picture of Subcutaneous Inoculation of Virulent Culture of Tubercle Bacilli· Guinea-pigs were inoculated subcutaneously with varying amounts of an emulsion of living tubercle bacilli in physiological salt solution The blood-picture in all cases was very much like the following, except that the number of days was necessary to reach the typical tuberculosis blood-picture varied with the amount used

TABLE 2.—BLOOD-PICTURE OF GUINEA-PIG VI, INOCULATED THREE MILLION STRONG EMULSION OF TUBERCLE BACILLI

Time with Reference to Inoculation	I	II	III	IV	V	VI	VII	VIII	Leukocytes,	Index	
Before	3	21	32	72	6	5			9,000	40	60
At time of	4	19	36	30	6	5			9,600	41	59
3 hours after	2	14	28	34	12	10			10,000	30	70
12 hours after	2	4	16	34	20	10	10	5	10,200	13	87
24 hours after	2	5	18	36	20	11	6	2	15,000	16	84
48 hours after	3	9	18	38	16	10	6		16,400	21	79
4 days after	3	12	38	34	8	3	2		14,000	34	66
8 days after	4	18	38	30	8	2			13,200	41	59
12 days after	8	22	39	24	5	2			13,400	49	51
18 days after	16	38	40	6					13,200	74	26
21 days after	23	45	32						12,800	84	16
25 days after	24	53	23						13,000	87	13

When the animal was killed the lungs and liver were found to be full of tubercles

These experiments seem to show that while the first result of the inoculation of the tubercle bacilli is to increase the number of neutrophils with the greater number of lobes in the nucleus, the prolonged effect of the bacilli is to use up the neutrophils which have the greater number of

lobes to the nucleus and leave only those with the fewer number of lobes The individual whose circulating blood contains an increased number of neutrophils with one or two lobes of the nucleus and a decreased number of neutrophils with four or five lobes is probably not in a state of resistance to the bacteria

5 The Effect of the Inoculation of Very Small Amounts of Emulsion of Living Tubercle Bacilli. A number of guinea-pigs were inoculated with such a small amount of the bacilli that when killed after several months no trace of tuberculosis was found in the organs of the animal In these cases the blood-picture showed a very slight increase in the number of lobes of the nucleus following the inoculation Then the blood-picture either rapidly returned to normal and remained normal or remained with a slight increase in the number of lobes of the nucleus

6 Blood on Agar with Tubercle Bacilli A drop of fresh flowing blood was placed on an agar plate and at one edge of the drop was placed a very small amount of tubercle bacilli The agar plate was kept in the incubator and smears made every five minutes from the side of the drop of the blood near the bacilli as well as from the side of the drop away from the bacilli The blood-picture showed an increase in the number of lobes of the nucleus of the neutrophils of the blood, which touched the bacilli, even after a period of five minutes, while the neutrophils of the blood away from the bacilli remained normal

Experiments in which washed leukocytes were used instead of normal blood gave the same result

7. The Effect of Contamination (*a*) Blood was drawn from the end of a finger purposely made dirty and slowly smeared on slides which had been handled and were not clean In all cases such smears gave a neutrophil blood-picture in which the number of the lobes of the nucleus had increased

(*b*) Blood was drawn from a clean finger and placed in small glass chambers which were not sterile and which were left open to the air of the incubator. Smears prepared from such blood after a period of five or ten minutes showed a decided increase in the number of lobes of the nucleus Neutrophils with as high as ten or twelve lobes to the nucleus were present while the blood from the same finger normally prepared or kept in sterile dishes in the incubator never contained neutrophils with a nucleus of more than five lobes

(*c*) One of the guinea-pigs inoculated with 2,000,000 weak emulsion of tubercle bacilli developed an open abscess at the point where the needle entered The smears prepared from the blood of this animal gave the following blood-picture, which shows an irregularity as well as an increase in the number of lobes of the nucleus of the neutrophils

TABLE 3—BLOOD-PICTURE OF GUINEA-PIG II, WHICH DEVELOPED ABSCESS FOLLOWING THE INOCULATION OF TWO MILLIONS OF TUBERCLE BACILLI

Time with Reference to Inoculation	I	II	III	IV	V	VI	VII	VIII	Leukocytes,	Index	
Before	4	21	36	30	5	44			10,000	43	57
At time of	3	21	35	30	6	5			10 200	41	58
3 hours after	2	16	32	30	8	6	3	3	12,000	34	66
12 hours after	2	14	30	20	14	10	6	4	14 000	31	69
24 hours after	3	20	30	18	13	7	5	4	13,500	38	62
48 hours after	2	21	32	26	10	6	3		14,000	39	61
4 days after	3	14	30	26	11	10	4	2	18,000	32	68
8 days after	1	10	33	28	13	7	5	3	16,000	27	72
12 days after		4	24	30	15	10	10	7	15 000	16	84
16 days after	12	24	30	20	10	4			22,000	51	49
18 days after		6	16	32	23	13	5	5	16,000	14	86
20 days after	4	10	18	34	19	11	4		17,000	23	77

Animal was killed — liver and lungs contained many tubercles

8 The Neutrophil Blood-Picture in Opsonic Index Work· Many of the slides studied were obtained through the courtesy of Dr W H Park of the New York Department of Health and others were prepared by us An emulsion of dead bacilli was used and the pipets were left in the incubator for fifteen minutes

All such smears gave a blood-picture in which the number of the lobes of the nucleus of the neutrophil was greatly increased Neutrophils with six, eight, ten, twelve and in one case sixteen lobes to the nucleus were found, while almost no neutrophils with one, two or three lobes were present

9 Effect of Inoculation with Snake Venom Inoculation of guinea-pigs subcutaneously with snake venom gave a neutrophilic blood-picture in which the number of the lobes of the nucleus was decidedly increased Many neutrophils contained nuclei of so many lobes that they had the appearance of rosettes The neutrophils of the bone-marrow showed the same change in quite as great an extent as did those of the circulating blood

CONCLUSIONS FROM EXPERIMENTS

1 The neutrophil is an organism which reacts quickly and definitely to its environment and this reaction is indicated by the number of lobes of the nucleus

2 The presence of neutrophils which have a nucleus of a greater number of lobes than normal indicates some reaction to a change in the environment such as the presence of a toxin or of bacilli

3 The presence of neutrophils which have a nucleus of a less number of lobes than normal indicates either that the neutrophils are being used up and so only those in the younger stage are left in the circulating blood or that the neutrophils entering the blood fail to undergo the metabolic or

morphologic change which causes the increase in the number of lobes of the nucleus and so remain in the one or two lobe form

4 The index shown by the neutrophilic blood-picture shows the condition of the neutrophils of the blood and in this way gives an insight into the condition of the subject

PULMONARY TUBERCULOSIS

Our observations in pulmonary tuberculosis were made on seventy-eight cases with a total of 315 separate blood-counts The period of time covered by our studies was three years, and this has made it possible to follow many cases of tuberculosis over a long period, which is very important in any effort to draw conclusions from observations made in regard to this disease

We wish to emphasize strongly the importance of studying the changes of the blood according to the clinical course of the disease and not according to the pathological conditions in the lungs, as has been done by the majority of observers who have reported on the changes in the leukocytes in tuberculosis, many of whom have followed the classification of Grawitz

We have classified our cases according to the stages of the National Association, and in addition to that, according to the clinical prognosis at the time of the first observation, and have followed these cases into their subsequent history, endeavoring to coordinate our blood findings with the clinical course

THE NUMBER OF LEUKOCYTES

The majority of authorities state that the leukocytes are not changed in uncomplicated tuberculosis, but are increased when secondary infection occurs, resulting in caseating lesions or cavity formation, or with exudative inflammation or in some of the complications, such as hemorrhage and enteritis

Kjer-Petersen[5] made a particularly careful study of the number of leukocytes in tuberculosis He comes to the conclusion that the extent of the lesion has no relation to the number of leukocytes, that in men in early stages the number is normal if there is no fever, and in third stage cases with no fever moderately increased but very variable — 6,000 to 15,000

In febrile cases there is some increase in all stages, and particularly those of continuous fever, which he attributes to mixed infection Other cases of pure tuberculosis with continuous fever are very variable but average low counts In women, as already stated, he found the count very variable

Stein and Erbmann,[38] Kjer-Petersen,[5] Applebaum[39] and Steffen[40] think a sudden increase in leukocytes important evidence of cavity formation Richard,[41] Bezançon, de Jong and de Serbonnes[42, 43] and Halbron[44] and Steffen[40] emphasize the importance of following the clinical course regardless of the pathology, and found a tendency to leukocytosis with the exacerbations of the disease

Claude and Zaky[45] obtained similar results in guinea-pigs, the leukocytes in the controls being increased and in treated animals less so Ullom and Craig[46] state that a decrease in the number of leukocytes in advanced cases is unfavorable Arneth also looks on a leukocytosis as favorable and states that a shifting to the left of his blood-picture is worse if the number of the leukocytes is low Craig[47] disagrees with Stein and Erbmann[38] in the significance of the increase of leukocytes with cavity formation They found often no leukocytosis in cases of cavity

Our own results in the enumeration of the total number of leukocytes coincide closely with those obtained by other observers, except that the average obtained in incipient cases and in the non-tuberculous cases is a little higher, 9,874 and 10,209 respectively There is a distinct increase in the number of leukocytes with the progression of the disease This is graphically shown in Chart 1 The striking difference between the non-tuberculous (10,209) and the moribund patients (26,300) corresponds with the reports of other observers of the frequent marked leukocytosis in dying patients The variations according to the stage, the clinical prognosis at the time of observation and the subsequent course of the disease show a distinct relationship between these factors and the number of leukocytes, which the chart shows better than description The fact that the figures shown for the prognosis correspond quite closely with those for the subsequent history, would appear to make the enumeration of the leukocytes in tuberculosis a procedure of more prognostic value than it is usually considered

Inasmuch as our cases have been followed in the majority of instances for more than two years since the blood-counts were made the data presented as to the subsequent history represent accurately the course of the disease

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38 Stein and Erbmann Deutsch Arch f klin Med, lvi, 323
39 Applebaum Berl klin Wchnschr, 1902, xxxix, 7
40 Steffen Deutsch Arch f klin Med, 1910, xcviii, 355
41 Richard Prov Med, 1908, xix, 205
42 Bezançon, deJong and de Serbonnes Arch d méd expér, 1910, xxii, 17
43 Bezançon et de Serbonnes Bull et Mem Soc Med d hôp d Paris, Ser 3, 1910, xxix, 232
44 Halbron Rev d la Tuberc, 1903, v, 319
45 Claude and Zaky Rev d la Tuberc, 1902, iv, 117
46 Ullom and Craig Am Jour Med Sc, 1905, cxxv, 386
47 Craig Tr Nat Assn Prev Tub, 1907, iii, 277

TABLE 4.—BLOOD COUNTS IN VARIOUS CLASSES OF TUBERCULOUS AND NON-TUBERCULOUS CASES

	No of Cases	No of Observ	Aver No Leuk	Per Cent Neut	Aver Arneth Indices		Per Cent L L	Per Cent S L	Per Cent Eos	Per Cent Bas
Not tuberc	9	37	10,209	64 4	54	46	17 5	11 8	5 8	0 53
Pulmon tuberc										
Incipient	15	50 54‡	9,874	72 4	64	36	14 4	9 0	3 7	0 52
Advanced	30	91-114	10,200	74 0	67	33	15 2	7 9	2 4	0 52
Far adv	20	91-101	13,218	77 9	75	25	13 9	6 2	1 5	0 44
Dying from tubercul other than pulmon *	4	8-9	26,300	78 5	66	34	17 1	4 1	0 29	0
Prognosis										
Good	19	62 79	9,398	71 8	60	40	14 8	9 1	3 7	0 53
Doubtful	18	77-87	11,591	78 0	73	27	13 7	5 8	2 0	0 32
Poor	29	84-99	12,486	77 1	72	28	13 4	7 5	1 6	0 35
Subsequent hist of tuberculous patient										
Improved	17	60-74	9,323	71 6	60	40	14 9	9 9	3 0	0 56
Dis station†	3	18	12,486	79 1	72	28	13 3	5 6	1 6	0 43
Dis progres	26	102-121	13,897	77 3	74	26	14 5	5 9	1 86	0 43

* Tuberculosis of kidney, of bladder, of psoas muscle and acute miliary

† Two of these cases were far advanced chronic cases

‡ Complete counts for every point were not invariably made

POLYNUCLEAR LEUKOCYTES

Almost all observers have found that when cases of tuberculosis showed a leukocytosis, it was usually of a polynuclear form and it is explained by the incidence of secondary infection. Experimentally, Achard and Loper[48] found that there was a primary increase in the polynuclears followed by an increase in the mononuclears.

Claude and Zaky[45] also found that the percentage of polynuclears was much less in treated animals with a tendency to localized lesions than in the control animals. Bezançon, de Jong and de Seibonnes[42] consider a polynucleosis as significant of acute and active disease and of great value in both prognosis and treatment, stating that all active treatment such as tuberculin, arsenic, superalimentation, etc., is contra-indicated if polynucleosis is present. They consider it a guide to the dosage of tuberculin similar to the opsonic index. Almost all observers consider an increased percentage of polynuclear an unfavorable sign.

In our own studies the percentage of neutrophils varies from 64.4 per cent in the non-tuberculous to 78.5 per cent in the moribund patients, and in general the percentage is higher the more advanced the disease and the more unfavorable the prognosis and subsequent course. All of these percentages are high in our observations, even the incipient cases showing a percentage of 72.4 per cent.

48 Achard and Loeper: Compt. rend. d. Soc. d. biol., 1900, lii, 1066, 1901, liii, 219.

The increase in the more unfavorable cases, however, is very marked and would seem to corroborate the observations of others that the leukocytosis of tuberculosis is due to an increase in the polymorphonuclears A high percentage of neutrophils would therefore seem from our observations to indicate an unfavorable prognosis, and this would be the more probable were an actual leukocytosis also present

ARNETH'S BLOOD-PICTURE

As already stated, unfavorable clinical reports on the value of Arneth's blood-picture in tuberculosis have been made by Paulicek,[20] Bourmoff and Brugsch,[21] Solis Cohen and Strickler[23] and Kagan [22] Many other observers, particularly those who have reported more recently, corroborate Arneth's findings in this disease Among them may be mentioned Klebs,[31] Sabrazès,[36] Dluski and Rospedishowski,[32] Pottenger,[49] Von Bonsdorf,[35] Bushnell and Treuholtz,[37] and Minor and Ringer [33]

We have already described our method of making the Arneth count and the meaning of the indices recorded in the tables While we appreciate the fact that the use of these indices is a marked departure from Arneth's own method, we have found from experience that they represent very accurately the main contention, i e , the shifting to the left in the nuclear blood-pictures It has been impracticable to tabulate the details of these counts and for that reason only the indices appear and the actual percentage of cells with their different number of nuclear segments is not represented

We feel that this in no way detracts from the practical value of the results presented, and we are anxious to emphasize our appreciation of these indices, or similar ones, as a valuable addition to the information that may be obtained from the differential leukocyte count The more cumbersome tables of Arneth would never come into general use, but their chief clinical value is retained in the indices which, because of their definite numerical form, can easily be incorporated into the results of every leukocyte count and probably will be, as soon as their value is more generally appreciated

Our results are seen in Chart 1, the left-hand number of the index being employed in the chart

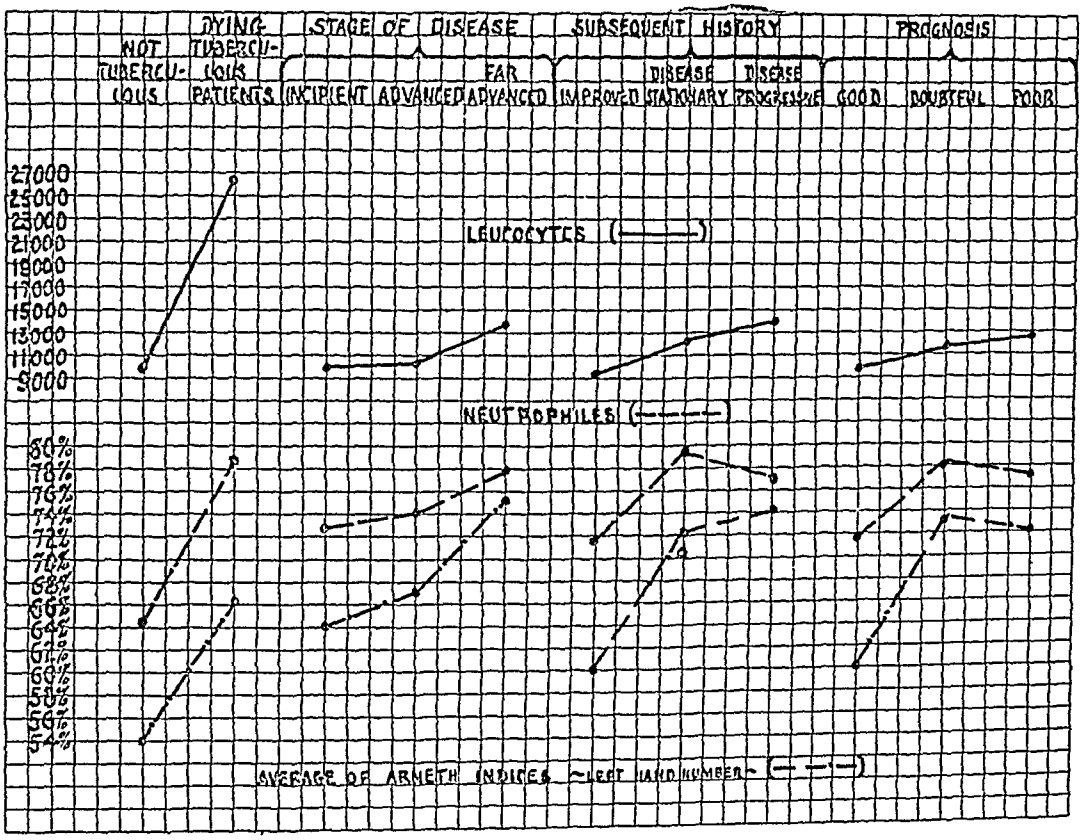
Our average index for the non-tuberculous cases was 54 · 46, and this corresponds closely with those obtained in a considerable number of observations on normal individuals In all other cases it will be seen that the left-hand number is much larger, and this represents the number of cells with one and two nucleus segments, plus one-half of the number having three segments It is evident how clearly the shifting to the left is demonstrated in our observations

49 Pottenger Jour Am Med Assn , 1909, lii, 1980

The degree of shifting also becomes more marked as the cases are more advanced until an average index of 75 25 is noted in the far advanced cases. Corresponding to this is the marked shifting noted in the cases with unfavorable prognosis and the subsequent clinical course

The relatively slight shifting in the four cases of moribund patients is surprising It is not to be expected from the progressive shift observed in cases with unfavorable course during the period of observation While it may be that there is a change in the nuclear blood-picture shortly before death, the number of cases of this sort which we have studied is so small that no definite deductions should be drawn from them

CHART I



From the general standpoint of diagnosis and prognosis, however, we feel that in the study of the nuclear blood-picture, we have obtained information which is of the greatest value in tuberculosis The changes noted are more constant than are any of the others in the blood and much more so than are many of the usual clinical signs and symptoms

In diagnosis the field of usefulness is limited because of the comparatively slight shifting in early cases, and the fact that it may occur in other conditions in which the general condition of the patient is below normal, our experience and that of others being that the shifting to the

left is simply a response to any deleterious influence in the body, especially the bacterial infections

In prognosis, however, both at the time of original examination and during the course of the disease, the degree of shifting to the left is an exceedingly sensitive indication of the resisting powers of the individual and of the progress of the disease

We have found that patients with very slight lesions but persistently presenting an unfavorable nuclear picture almost invariably do badly, and that, on the contrary, those with extensive lesions but fairly good nuclear picture show a marked tendency to resist the disease successfully. Moreover, during the clinical observations of a case, its real progress in one direction or the other can usually be more accurately anticipated by the changes in the nuclear picture than by any other clinical means

Even clinical apparent cures, as Arneth well claims, are insecure unless the nuclear picture has come nearly to approach the normal, and our experience has made us very reluctant to advise a return to work and less favorable surroundings in such cases, while such return may be allowed with considerable confidence when a healthy blood-picture is found

ARNETH'S BLOOD-PICTURE AS A GUIDE TO SPECIFIC TREATMENT

Arneth asserts that his blood-picture is of great value both as a guide to dosage in tuberculin and also as a test for the effect of the treatment He also considers it of value in deciding the question of the necessity for secondary courses of treatment with tuberculin Uhl[50] has found it of value in a similar way Von Bonsdorf also used it as a guide for dosage, and notes a negative phase in the blood-picture after tuberculin similar to that of the opsonic index Arloing and Genty[51] have compared the blood taken with the agglutinating power of the serum and also with the results of treatment with Maragliano's and Marmorek's serums and find a general correspondence in the results Rover[52] also corroborates these results with Marmorek's serum Kaufmann,[53] on the contrary, found no relation between the effects of Marmorek's serum or the clinical course and the changes in Arneth's blood-picture

In our own work we at first attempted to use Arneth's blood-picture as a guide to tuberculin dosage, and for a while it seemed as though results were encouraging, but later experience has demonstrated to us that it is of little or no value, and that the usual clinical guides are much more consistent and delicate than any changes we have found in the leukocytes

50 Uhl· Beitr z klin d Tuberk, 1906, vi, 249
51 Arloing and Genty Jour d phys et d path gèn, 1910, xii, 236
52 Rover Beitr z Klin d Tuberk, 1906, v, 299
53 Kaufmann Beitr z Klin d Tuberk, 1908, xi, 315

THE LYMPHOCYTES

In a general way, the majority of observers have noted a change in the lymphocytes inversely proportionate to the neutrophils In consequence, a diminishing number of lymphocytes would be considered unfavorable and an increase correspondingly favorable Da Costa[10] asserts that occasionally the leukocytosis of advanced disease is due to lymphocytes Warthin[54] also noted this symptom in chronic cases, as does Cabot[6] Ailoing and Genty,[51] Richard,[41] Bezançon, de Jong and de Serbonnes,[42] Halbron,[44] Sabrazès,[36] Steffen,[40] Ullom and Craig[46] all consider that an increased percentage is favorable Steffen[40] and Bezançon, de Jong and de Serbonnes[42] lay especial stress on its favorable significance during periods of improvement

Experimentally, Achard and Loeper[48] found that secondarily in guinea-pigs there was a lymphocytosis following a polynucleosis Claude and Zaky[45] found that in controls the lymphocytes were diminished and that in chronic cases and treated patients the large mononuclear cells were increased

Webb and Williams[9] lay stress on the increase of the large mononuclears in improving cases and as an effect of altitude They think that the beneficial effects of altitude in tuberculosis may be attributable to this increase

In our own results we have separated the lymphocytes into the large lymphocytes and the small lymphocytes with the following results

THE LARGE LYMPHOCYTES

The proportion of these cells which we have found in our counts is fairly constant in all stages and all degrees of progression of the disease No apparent relationship to the clinical data can be made out from the slight variations in percentages recorded in Table 1 and charted in Chart 2 It would seem therefore that no clinical importance is to be attached to these cells in tuberculosis

THE SMALL LYMPHOCYTES

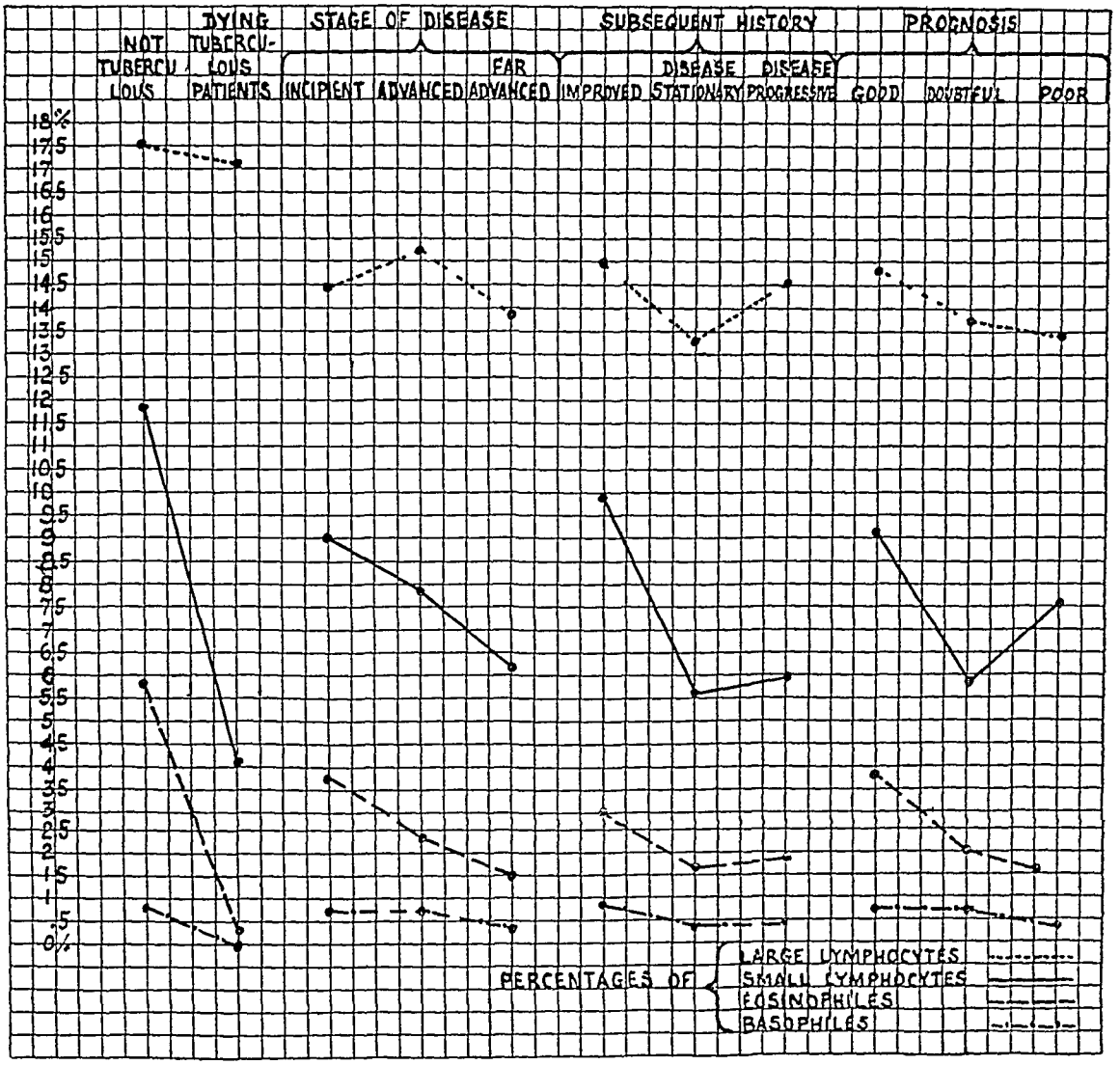
In sharp contrast to the large lymphocytes a very definite and interesting relationship appears to exist between the small lymphocytes and the clinical manifestations This is apparent in Table 4 and is shown very graphically in Chart 2 With the greater extent of the lesion and the unfavorable progress of our cases there is a progressive diminution in the percentage of the small lymphocytes In the incipient cases, those with good prognosis, those whose subsequent history show improvement and in the non-tuberculous cases the percentage of the cells are found to be uniformly high, varying from 9 0 per cent to 11 8 per cent On the

54 Warthin Med News, 1896, lxviii, 89

other hand, the more advanced and unfavorable cases show percentages from 4 1 per cent to 6 2 per cent

The moderately advanced cases and those with doubtful prognosis standing midway between the other classes 7 5 per cent to 7 9 per cent It is evident that in our cases the increased percentage of the neutrophils in unfavorable cases has been largely at the expense of the percentages of the small lymphocytes

CHART II



THE EOSINOPHILS

A good deal of emphasis has been laid on the rôle of the eosinophils in the circulating blood as a guide to the clinical condition of the cases of tuberculosis In general, in acute progressive cases with secondary infection, the eosinophils have been observed to be diminished or absent and to reappear or increase during the periods of improvement or in early and favorable cases Such is the opinion expressed by Naegeli,[4] Ewing,[7]

Swan,[55] Holmes,[56] Arloing and Genty,[51] Sabrazès,[36] Cabot,[6] Da Costa,[10] Zappert,[57] Galbraith,[58] Applebaum, Richard,[41] Steffen[40] and others Bezançon, de Jong and de Serbonnes[42] think that the presence of the eosinophils indicates good resisting power and note their increase in improving cases especially in chronic inactive cases in which they consider that the tubercle bacillus lives in the body as a parasite

Holbron[44] asserts that they are diminished in advanced cases and absent in all cavity cases Neusser[59] also considers that the increase in eosinophils denotes an immunity to the tubercle bacillus

Webb and Williams[9] noted a very slight decrease in advancing cases which, however, was not distinct Ullom and Craig,[46] Solis Cohen and Strickler[22] and Craig[47] found no relation between these cells and the clinical course of the disease Experimentally, Claude and Zaky[45] and Achard and Loeper[48] found that these cells were diminished in control cases, but reappeared subsequently if the animals lived, and in chronic cases they were increased

Numerous authorities, including Ewing,[7] Cabot,[6] Bischoff,[60] Rieder[61] and Bodkin,[62] note an increase in the eosinophils after the administration of tuberculin

Our results coincide with the majority of observers, and we have found that with the progression of the disease these cells become less and less numerous until they almost entirely disappear from the blood in the terminal stages

Our results show 5 8 per cent in non-tuberculous cases and 3 7 per cent in the incipient cases and those with good prognosis This percentage is reduced to 1 5 per cent in the far-advanced patients and 0 29 per cent in the moribund patients Chart 2 shows this relationship very clearly

THE BASOPHILS

We have found no reference in literature as to the behavior of the basophil leukocytes in tuberculosis The small number of these cells found in the blood renders valueless conclusions drawn from the count of from only 100 to 200 cells The indications, however, are that they do not vary appreciably in the various phases of tuberculosis and that they have no clinical significance

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55 Swan Jour Am Med Assn, 1904, xlii, 696, Swan and Karsner New York Med Jour, 1907, lxxxv, 539

56 Holmes Med Rec, 1896, l, 325, 1897, li, 369, Jour Am Med Assn, 1897, xxix, 828

57 Zappert Ztschr f klin Med, 1893, xxiii, 227

58 Galbraith Brit Med Jour, 1903, i, 600

59 Neusser Wien klin Wchnschr, 1894, vii, 727

60 Bischoff *Inaug* Dissert, Berlin, 1891

61 Rieder Atlas der klinische Mikroskopie des Blutes, Leipsic, 1907, F C W Vogel, Beitr z Kenntniss d Leukocytosis, Leipsic, 1892, F C W Vogel

62 Bodkin Deutsch med Wchnschr, 1892, xviii, 321

COMPOSITE TUBERCULOSIS BLOOD-PICTURE

In order easily to appreciate the clinical significance of our findings, we have arranged them in the form of composite blood-pictures for each of the more important features of the disease, in Table 5

TABLE 5.—BLOOD COUNTS IN VARIOUS CLASSES OF TUBERCULOUS AND NON-TUBERCULOUS CASES

I NON-TUBERCULOUS CASES

Nine cases — thirty-seven counts

Total Number	N	L L	S L	E	B	Index
10,209	64 4	17 5	11 8	5 8	53	54 56

II INCIPIENT TUBERCULOSIS

Fifteen cases — fifty-four counts

Total Number	N	L L	S L	E	B	Index
9,874	72 4	14 4	9	3 7	53	64 36

III ADVANCED TUBERCULOSIS

Thirty cases — 114 counts

Total Number	N	L L	S L	E	B	Index
10,200	74	15 2	7 9	2 4	52	67 33

IV FAR-ADVANCED TUBERCULOSIS

Twenty cases — 101 counts

Total Number	N	L L	S L	E	B	Index
13,218	77 9	13 9	6 2	1 5	44	75 25

V MORIBUND PATIENTS

Four cases — nine counts

Total Number	N	L L	S L	E	B	Index
26,300	78 5	17 1	4 1	29	0	66 34

VI CASES WITH GOOD PROGNOSIS

Nineteen cases — seventy-nine counts

Total Number	N	L L	S L	E	B	Index
9,398	71 8	14 8	9 1	3 7	53	60 40

VII CASES WITH POOR PROGNOSIS

Twenty-nine cases — ninety-nine counts

Total Number	N	L L	S L	E	B	Index
12,486	77 1	13 4	7 5	1 6	3	72 28

VIII CASES WHICH SHOWED SUBSEQUENT IMPROVEMENT

Seventeen cases — seventy-four counts

Total Number	N	L L	S L	E	B	Index
9,323	71 6	14 9	9 9	3 0	56	60 40

IX CASES WHICH SUBSEQUENTLY DID BADLY

Twenty-six cases — 121 counts

Total Number	N	L L	S L	E	B	Index
13,897	77 3	14 5	5 9	1 86	43	74 26

PNEUMONIA

A review of the literature concerning the behavior of the leukocytes during lobar pneumonia shows that the presence of leukocytosis in this disease has been recognized from the very beginning of blood examinations Cabot[6] states that the leukocytosis when marked indicates good resistance on the part of the individual or a severe infection, and that a slight leukocytosis or normal leukocyte count indicates a poor resistance or a mild infection He considers the absence of leukocytosis a very bad

sign but its presence of no significance for either good or bad In 842 cases ninety showed no leukocytosis and of these eighty-three were fatal

Cabot's ideas are similar to those expressed by Ewing,[69] Naegeli,[4] Da Costa,[10] Buchanan,[63] and others Tuik[2] states that the leukocytosis bears no relation to the severity of the disease, and that if it continues after crisis it indicates delayed resolution or some complication

Rieder[61] states that it has no relation to the height of the fever Von Limbeck[64] states that the leukocytosis is in proportion to the lung involvement This contention has been disproved by numerous observers Von Jaksch[65] made a careful study, showing the importance of leukocytosis from the standpoint of prognosis and advocated artificial means to produce leukocytosis such as drugs, local abscess formation, etc These ideas are now obsolete

EXPERIMENTAL EVIDENCE

Tschistovitsch (quoted by Von Limbeck[64]) experimented with guinea-pigs and found that an injection of highly virulent cultures of pneumococcus produced no leukocytosis and the animals died Weaker cultures produced leukocytosis and the animals recovered

Rieder[61] inoculated guinea-pigs intraperitoneally with pneumonia sputum and obtained subnormal leukocyte count and subnormal temperature Williamson,[66] by injections of pneumococcus cultures in guinea-pigs, obtained a leukocytosis of varying intensity followed by a diminution in the number of leukocytes He also noted no relation between leukocytosis and the course of the disease

CLINICAL STUDY

Our studies of the leukocytes in pneumonia have failed to reveal the definite clinical relationships that we found in tuberculosis

Forty cases were studied and on these 131 separate blood counts were made Almost the entire number were cases of lobar pneumonia but a few of bronchopneumonia are included All of the observations were in adults

In attempting to trace the connections between the blood counts and the clinical findings, we have analyzed the cases according to the extent of involvement, the clinical severity of the infection, the method of defervescence, the duration, the final results and the complications

Our results in their relation to all of these factors are tabulated in Table 6

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63 Buchanan The Blood in Health and Disease, London, 1909, H Frowde
64 Von Limbeck Grundriss einer klinischen Pathologie des Blutes Jena, 1896, G Fischer
65 Von Jaksch Ztschr f klin Med, 1893, xxiii, 187, Centralbl f klin Med, 1892, xiii, 81
66 Williamson Beitr z pathol Anat und Allg Path, 1901, xxix, 41
69 Ewing New York Med Jour, 1893, lviii, 713

TABLE 6.—OBSERVATIONS IN LOBAR AND BRONCHOPNEUMONIA DURING THE ACUTE ATTACK

	No of Cases	No Observ	Aver No Leuk	Per Cent Neut	Aver Arneth Indices		Per Cent L L	Per Cent S L	Per Cent Eos	Per Cent Bas	Per Cent Myelo
Involvement											
One lobe	24	91-92	17,058	77	67	33	16 8	4 6	1 2	0 27	0 11
Two lobes	16	35-39	18,012	76 5	56	44	17 6	4 1	1 5	0 23	0 04
Severity											
Mild	11	47-49	17,634	76 9	66	34	16 5	4 6	1 6	0 25	0 09
Moderate	13	45-46	14,532	72 9	63	37	19 5	5 3	1 8	0 42	0 08
Severe	11	28-29	20,250	81 8	62	38	15	3 0	0 08	0 3	0 07
Defervescence											
Crisis	21	71-74	16,355	74 9	64	36	17 6	5 2	1 9	0 23	0 14
Lysis	8	30-32	17,028	77 5	64	36	17 5	3 6	77	0 48	0
Duration											
Up to six days inc	4	10	16,660	72 1	66	34	18 7	7 8	1 4	0	0 13
Seven days and over	18	17-18	16,912	76 4	65	35	17 4	4 5	1 2	0 30	0
Result											
Cured	12	40	16,265	77 6	63	37	16 5	4 9	0 89	0 077	
Died	10	27	21,040	80 9	60	40	15 6	3 2	0 12	0 057	0 18
Delayed resolution	11	46 50	15,255	73 3	66	34	18 7	4 9	2 4	0 53	0
Complications											
Empyema	3	10	16,600	85 6	61	39	11 3	3 0	0 008	0	0
Pericarditis, etc	6	10-11	17,960	72 8	66	34	22 5	3 7	0 66	0 26	0
AFTER SUBSIDENCE OF ATTACK											
Resolution											
Good	11	20	12,930	73 0	59	41	19 2	6 2	1 4	0 10	0
Delayed	6	20-22	12,995	64 4	64	36	23 3	7 3	3 93	0 77	0 25

In addition, the observations on the leukocytes after the acute infection was over have been studied in respect to the promptness of resolution in the lungs and these results are also included in the table

TOTAL NUMBER OF LEUKOCYTES

The usual leukocytosis expected in pneumonia was present in our cases but was not as marked as is often seen The number of leukocytes varied from 15,000 to 20,000 in all classes of cases excepting in the series of ten patients who died, in which the average of twenty-seven counts was 21,040 This is noteworthy because these results disagree with the more usual finding that a high leukocytosis indicates a good prognosis and a low one the reverse Our series is too small to enable us to draw definite conclusions in this regard but the results are nevertheless suggestive

The usual diminution in leukocytosis is noted after the defervescence This is not so very marked, the counts averaging about 13 000 Most of these counts were made in the first week after defervescence and indicate a gradual return toward the normal leukocyte count

In order to ascertain whether there was much variation in the leukocytosis of pneumonia in various years corresponding to the rather general opinion that there is a marked difference in the virulence in this disease at different times, we have collected the records of the leukocyte count in lobar pneumonia for five years, 1904 to 1908 inclusive, of the First Medical Division of Bellevue Hospital Thus 514 cases are studied and the results are tabulated in Table 7

TABLE 7.—LEUKOCYTE COUNTS IN LOBAR PNEUMONIA DURING ACUTE ILLNESS

Counts Between	1904 %	1905 %	1906 %	1907 %	1908 %
PATIENTS WHO RECOVERED					
0-10,000	5	15	7	7	13
11,000-20,000	41	45	33	58	52
21,000 30,000	30	38	43	28	20
31,000 40,000	22	2	15	7	13
41,000 50,000	2	0	2	0	2
Average Number of Leukocytes	22,501	18,375	22,865	19,243	19,208
PATIENTS WHO DIED					
0-10,000	17	10	25	16	11
11,000-20,000	46	53	47	51	54
21,000 30,000	25	25	18	25	28
31,000 40,000	4	12	8	8	7
41,000 50,000	8	0	2	0	0
Average Number of Leukocytes	19,652	19,938	18,216	18,024	18,218

SUMMARY FOR THE FIVE YEARS OF 514 CASES

	Number		Per Cent	
	Recovered	Died	Recovered	Died
0-10,000	26	39	10	16
11,000-20,000	123	123	46	50
21,000 30,000	85	59	31	24
31,000 40,000	32	19	12	8
41,000-50,000	3	5	1	2
Total	269	245	100	100
Average Number of Leukocytes	20,444	18,827		

From this table it does not appear that there is any great variation in the various years, certainly none from which any valuable inference could be drawn

These results also do not demonstrate any definite relationship between fatality and low leukocyte counts The average for the entire 514 cases showed 20,444 for the patients who recovered and 18,827 for those who died These cases are all uncomplicated and the counts of course were made by numerous observers

DIFFERENTIAL COUNT

Cabot,[6] Ewing,[7] Da Costa,[10] Turk,[2] Rieder[61] and others all find that the leukocytosis of pneumonia is due to the increase of the neutrophils Turk, who has studied the differential count in pneumonia most thoroughly, states that the neutrophils are increased in proportion to the leukocytosis, that they fall with the crisis but not with a pseudocrisis, that the large mononuclear cells and transitionals vary with the neutrophils, that the lymphocytes may be increased, normal, or diminished in number but that after a crisis they are usually increased, that eosinophils are absent or few during the fever but that their presence is favorable and that after a crisis they are distinctly increased, their reappearance in the blood often being evidence of beginning resolution Myelocytes may appear if the infection is very acute

Most authorities agree in general with Turk's observations Becker[67] states that he has never found any eosinophils present in fatal cases Loeper[68] states that if the percentage of neutrophils is over 90 per cent the case is almost invariably fatal

Our observations show that the neutrophils are invariably increased excepting after defervescence, that they vary from 72 to 77 per cent in all classes of cases excepting in the very severe infections in which they were 81 8 per cent In patients who died they were 80 9 per cent and in those who had empyema as a complication, 85 6 per cent

It would appear therefore that an excessive increase in the percentage of neutrophils indicates a very severe infection In the lymphocytes our studies fail to reveal any clinical evidence of value The percentage of large lymphocytes varies from 15 to 23 3 per cent and the small lymphocytes from 3 to 7 3 per cent

In the cases of severe infection the percentage of large lymphocytes was comparatively low and higher in those with delayed resolution after defervescence

In the eosinophil cells the blood counts during the acute illness showed nothing of note, the percentage being normal throughout In six cases of delayed resolution, however, the average percentage of these cells in twenty counts was 3 93 This moderate increase is in accord with the results of other observers in such cases and appears to have some definite relationship to the condition in the lung

The basophils and myelocytes were observed in very small numbers and are apparently of no clinical significance

67 Becker Deutsch med Wchnschr, 1900 xxvi, 558
68 Loeper Arch d med exper 1899 xi, 724

THE ARNETH BLOOD-PICTURE

Very few studies of Arneth's blood-picture of pneumonia have been reported Arneth reports on sixteen cases and notes greater variations in his blood-picture between different cases of pneumonia than in any other infectious disease There is regularly a marked shifting to the left which may come immediately with the onset or may come on gradually and increase to its highest point just before or after crisis

Complications, according to Arneth, bring out a new and increased shifting to the left The blood-picture may return to the normal quickly, corresponding to a rapid resolution, or may continue to get worse at the time of the crisis, even though the total leukocyte count may fall

Cases defervescing by crisis are more apt to return to normal quickly and those by lysis more slowly In delayed resolution and chronic interstitial pneumonia, a shifting to the left with a normal or diminished leukocyte count may persist for months Arneth draws no clinical conclusions of value from his own results

The observations on our cases show a moderate shifting to the left in the Arneth blood-picture to be a constant factor in our cases of pneumonia This shifting is less marked than in the more advanced cases of tuberculosis and does not vary in any definite relation to the clinical aspects of the cases studied, the index varying from 60 40 to 67 33

Very quickly after defervescence the index tends to go back to the normal if good resolution is established The average index of all such cases studied was 59 41, but these counts were made usually within the two or three days after defervescence, and we have noted in some cases a return to absolute normal nearly coincident with the signs of complete resolution in the lungs

In the six cases of delayed resolution, however, the average index was 64 33, showing the continuation of the shifting to the left in such cases after the fever had subsided, the whole picture in such cases being very similar to that of moderately advanced tuberculosis

It is to be noted that the least shifting to the left of any clinical group of cases was in the ten patients who died, the average index being 60 40

An unusual average index is noted in Table 2, under the group of sixteen cases with involvement of two lobes

This average does not accurately represent the usual condition of affairs in such cases, but in this series is markedly modified by several observations on one case, which showed a very unusual blood-picture with a marked shifting to the right This patient died and autopsy showed a marked purulent bronchitis in addition to the unresolved pneumonia

The index above noted, 60 40, for the patient who died, is also influenced by this case, which cannot be considered at all representative of the usual blood-picture found in pneumonia

This case is deserving of further consideration as tending to corroborate our experimental observations, that in the presence of a purulent infection the shift may be to the right and the fragmentation of the nucleus becomes very marked in a considerable number of the neutrophils, even up to seven or eight segments

In general, we have found the determination of Arneth's blood-picture of practically no clinical value in pneumonia

The composite blood-picture of pneumonia from our results would be

Total Number	N	L L	S L	E	B	M	Index
17,058	77	16 8	4 6	1 2	0 27	0 11	67 33

The only other composite blood-pictures worthy of separate note in our findings are

AFTER DEFERVESCENCE WITH GOOD RESOLUTION

Total Number	N	L L	S L	E	B	M	Index
12,930	73	19 2	6 2	1 4	0 1	00	59 41

AFTER DEFERVESCENCE WITH DELAYED RESOLUTION

Total Number	N	L L	S L	E	B	M	Index
12,995	64 4	23 3	7 3	3 93	0 77	0 25	64 36

CONCLUSIONS

Pulmonary Tuberculosis

1. The study of the leukocytes gives valuable information in the prognosis and clinical course of pulmonary tuberculosis

2 In diagnosis of incipient cases it is of no assistance but in differential diagnosis of whether more acute pulmonary lesions are due to tuberculosis or some other infection it is sometimes helpful

3 Arneth's differential neutrophil count is important in tuberculosis

4 In general, the following changes in the leukocytes occur in cases of pulmonary tuberculosis which are progressively doing badly or are in an exacerbation of the disease

(*a*) A leukocytosis

(*b*) An increased percentage of neutrophils

(*c*) A diminished percentage of small lymphocytes

(*d*) A diminished percentage of eosinophils

(*e*) A marked shifting to the left of Arneth's blood-picture Conversely, changes in the opposite direction in any of the above factors are favorable

Pneumonia

1 Leukocytosis occurs as frequently in fatal cases as in those of recovery

2 This leukocytosis is due to the increased number of neutrophils

3 When this increase of neutrophils is excessive a very severe infection is indicated

4 Arneth's differential neutrophil count shows a constant shifting to the left in pneumonia, but it bears no relationship to the clinical course of the disease

BOOK REVIEW

NEPHRITIS AN EXPERIMENTAL AND CRITICAL STUDY OF ITS NATURE, CAUSE AND THE PRINCIPLES OF ITS RELIEF By Martin H Fischer The 1911 Cartwright Prize Essay of the Association of the Alumni of the College of Physicians and Surgeons, Medical Department of Columbia University, New York First Edition Cloth. Price, $2 50 Pp 201 New York John Wiley & Sons, 1912.

After a careful reading of Fischer's latest book, the reviewer is forced to the unwelcome conclusion that its title page should proclaim it, not an experimental and critical study, but a speculative and uncritical study The author's previous publication on edema, while exhibiting the spirit of the special pleader, rather than the judicial and conservative student, nevertheless called attention to the rôle of the tissue colloids in the production of dropsy, and served notice that the physiochemical standpoint must not be neglected in the interpretation of pathological phenomena Now he proclaims in effect that there is no other standpoint Physical chemistry affords to the author the sole and sufficient explanation for all the phenomena of nephritis In his introductory paragraph he writes

> To render our argument clear, we will at once state our general conclusion
>
> All the changes that characterize nephritis are due to a common cause—the abnormal production or accumulation of acid in the cells of the kidney To the action of this acid on the colloidal structures that make up the kidney are due the albuminuria, the specific morphological changes noted in the kidneys, the associated production of casts, the quantitative variations in the amount of urine secreted, the quantitative variations in the amounts of dissolved substances secreted, etc

These phenomena—albuminuria, morphological changes, and disturbances of secretion—he discusses in successive chapters, and ends with a fourth chapter on the treatment of nephritis

That a professor of physiology in the twentieth century should begin "an experimental study" by postulating his conclusions is somewhat startling, that he should complete a critical study without reference to the bulk of the important literature of the disease is amazing Instead of a thorough discussion of the relation of his theory to the ideas of the best clinical students of nephritis, such as Senator, for instance, or to the mass of accumulated observations on experimental nephritis, he contents himself with a criticism of conceptions now held only by the least educated of physicians This is setting up a man of straw, only to knock it down again—to demonstrate one's prowess His experiments are few and of the simplest kind, and yet upon them he bases a theory of the common origin of the most varied and complex derangements of function and structure He himself, however, states plainly on the first page how little exacting he considers the requirements of scientific demonstration

> Yet the persistence of the term nephritis, in spite of our daily efforts in medicine to become more precise, seems to be not without reason, it is the one term by which we are enabled to express the fact that the albuminuria, the anuria, etc, nearly always appear as *associated* phenomena But from such a constancy in association we are enabled to draw an important conclusion—*they must all have a common cause*

Certainly, we are not enabled to draw any such conclusion, if we have the rudiments of a scientific education Constancy of association should indeed suggest to the inquiring mind a common cause, but its demonstration demands rigorous experiment and painstaking investigations into the possibility that unlike causes may yet produce like effects Dr Fischer might with profit study those postulates of Koch, through the fulfillment of which bacteriology has made its demonstration of causes convincing and in the highest degree productive of practical results

As might be expected from such a beginning, the author proceeds with his argument on the basis that whenever the facts conflict with his theory, so much the worse for the facts I will cite instances On page 53 he states that "Albuminuria is the constant *accompaniment of salt-starvation,*' complete or only of sodium chlorid No more complete salt-starvation experiments have ever been reported than those of Goodall and Joslin[1] They fed two men on an ash free diet for eleven and thirteen days, respectively Their urine was acid throughout, but never contained the least albumin nor a single cast, though the NaCl output was reduced to its minimum

On page 49 he cavalierly disposes of paroxysmal hemoglobinuria in a footnote, as another instance of acid effect, without the least reference to the elaborate demonstration of the hemolytic mechanism in these cases by Donath and Landsteiner In fact, Meyer and Emmerich[2] showed that while the red cells in these patients are less resistant to acids than normal red cells, they are actually more resistant to the specific hemolysis of their blood

On page 25 he speaks of "*the uniformly higher titration acidity of the urine in nephritis*" Throughout the chapter on albuminuria, the acid argument is at its best, yet he has not made the simplest verification of his theories by examining the urine of a series of nephritics Had he done so, he would have found that a number have albumin in a neutral or alkaline urine, and that alkali may be given sometimes with and sometimes without the least effect on a marked albuminuria, as is well reported by v Hoesslin[3] in a really objective study of this question which the reviewer has corroborated personally

On page 119 he says "Yet, other things being equal, the absolute amount of any dissolved substance secreted by the kidney must be the greater, the larger the absolute amount of water secreted by the kidney in any unit of time" He seems never to have heard of the most important studies of kidney function which have appeared in years, those of Schlayer and Takayasu[4] They showed that the excretion of lactose, for instance, is wholly uninfluenced by the amount of water excreted The same seems to hold good for Rowntree's sulphophenolphthalein

Not to multiply instances, one need only turn to his own self-contradictions On page 126 he cites the organic acids of fruits and sour wines as possible causes of nephritis, and on page 128 tells how successfully a diet rich in fruits and vegetables counteracts the tendency of the body to become acid

It is in the chapter devoted to the explanation of the morphological changes of nephritis, however, that facts are absolutely thrown to the winds This is natural, since the rigid and unimaginative data of anatomy are usually distasteful to a speculative mind At the outset he remarks that, "If we will but free our minds from the erroneous conclusions to which the temptations of elaborate fixing and staining methods and high power microscopes have led us, it is an easy matter to see that all the morphological changes that occur in a kidney, the seat of an acute or chronic nephritis, are fundamentally simple in character, and that they are easily brought into connection with the clinical manifestations of the disease" One rubs his eyes at this and wonders whether he is reading "Alice in Wonderland" Of course, if one can discard all his knowledge of the histological

1 Goodall and Joslin THE ARCHIVES INT MED, 1908 i, 615
2 Meyer and Emmerich Deutsch Arch f klin Med, 1909, xcvi, 326
3 Von Hoesslin Deutsch Arch f klin Med, 1911, cv, i, ii, 147
4 Schlayer and Takayasu Deutsch Arch f klin Med, 1910, xcviii, 17

complexity of the kidney in health and disease, it becomes delightfully simple, so does life, if one discards all the acquisitions of civilization, but unless he lives with aboriginal savages, he will be put in an insane asylum

Somewhat further, on page 60, one feels that he is witnessing the performance of a scientific prestidigitateur, when the author closes a disingenuous discussion of chronic interstitial nephritis with the words "In thus getting the chronic interstitial forms of nephritis back into a group with the frankly parenchymatous forms" How disingenuous his argument is he reveals himself On page 59 one reads "In chronic interstitial nephritis the ultimate picture is produced through a gradual but complete destruction of one piece after another of the kidney parenchyma, with replacement of the defect with connective tissue *The portions of kidney involved in this localized destruction of kidney parenchyma show all the signs characteristic of parenchymatous nephritis* For the present it is sufficient to merely emphasize the fact that *a chronic interstitial nephritis is in essence also a parenchymatous nephritis* " Turn to page 95 "*So far as water output is concerned, the patient with chronic interstitial nephritis is simply not nephritic* If a patient without these signs and symptoms dies, and on the autopsy table we find the small kidneys that we diagnose anatomically as chronic interstitial nephritis, then the parenchyma cells of the kidney —the only parts of the kidney that are concerned with the physiological function —are also found looking normal The small, red kidneys are, except for size, normal kidneys" Even if we should grant him that glomeruli are but creations of the histologist's imagination and undeserving the recognition of a physiologist what can one say to the statement that the tubular epithelium in a contracted kidney is normal? There is only one charitable assumption—that the author never saw a section of one under the microscope Yet he writes a book entitled "Nephritis!"

One who can thus dispose of all anatomical obstacles naturally makes short shrift of the experiences of the clinician, though with a charming humor and condescension he frequently speaks of "we clinicians" All Widal's work on salt retention in relation to edema and the value of salt restriction in the diet, so amply corroborated by many well conducted experiments, he dismisses unceremoniously The need for adjustment of the water intake in acute nephritis to the ability of the kidney to excrete it, which we recognize since von Noorden's studies, is dismissed with the statement that "*the intake of water should never be restricted*" Does he conduct careful experiments on nephritic patients to justify such radical teaching? Not at all He ties rabbits on a board so as to interfere with respiration, gets an albuminuria, calls this nephritis, and treats it successfully with salt! Finally, to make his assurance doubly sure he says "In order to satisfy myself as to whether sodium chlorid really has any such specific action in the production of edema, I decided to test the matter out in a way that had not yet been done, and which was freer from objection than the experiments to determine this point that have been made on mammals" And then he describes experiments on frogs poisoned with uranium nitrate and hung in water, to show that they developed edema more than in salt solution He does recite the histories of twelve patients treated according to his theories Instead of carefully recorded hospital studies, they read like the cures of the nostrum venders Six are cases of eclampsia or pregnancy nephritis, which pursued the usual course after emptying the uterus One died from uremia and is wrongly diagnosticated as generalized arteriosclerosis at 16 years The description of the kidneys shows them to have been secondary contracted kidneys Two cases of scarlatinal nephritis and one subsequent to tonsillitis carry no conviction of the relation of treatment to recovery Cases 10 and 11 must be admitted as highly suggestive of benefit from the measures employed

The reviewer is convinced that it is a public duty to show the essential faults of such a book as this because its superficially scientific air makes it impose the

more easily on the practicing physician, who may at once adopt its recommendations Experiments on edematous human beings are far more scientific than experiments on frogs, when the effects of therapeutic measures for human nephritis are in question A book which teaches the opposite is a vicious book, which should be condemned by physiologist and clinician alike Notwithstanding Dr Fischer's physico chemical studies, nephritis remains, not a problem, but a group of problems to be solved by the united efforts of workers along many possible lines of investigation,

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A CLINICAL AND HISTOLOGICAL STUDY OF A CASE OF PAGET'S DISEASE OF THE BONES WITH MULTIPLE SARCOMA FORMATION

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MONTREAL

PART I BY L S FOSTER

Complete reports of bone changes of a rarefying nature, with marked evidence of overgrowth and deformity, corresponding exactly with the classic description of the disease known as osteitis deformans are exceedingly rare

The late Sir James Paget, in his graphic, masterly and original study, was the first to isolate this type from the general group of bone diseases, claiming for it a clinical and a pathological recognition as a distinct, morbid process, and, in the *Medico Chirurgical Transactions* for the year 1877, gave the histories of five cases Five years later he had gathered together twenty-three cases and outlined a clear and concise clinical picture, to which subsequent observers have made few additions of importance

"The disease is one beginning in advanced life, usually affecting many bones most frequently the long bones of the lower extremity the clavicle and the vault of the skull The bones enlarge and soften and those carrying weight or bearing much muscular traction become unnaturally curved and misshapen The disease is slowly progressive and is attended with pains in the affected bones varying in severity and usually described as rheumatic or neuralgic in character The general appearance, postures and movements of the patients are so alike that these alone might often suffice for diagnosis The most characteristic features are the loss in height, indicated by the low position of the hands the stooping with round shoulders the head held forward with the chin raised and the chest sunken towards the pelvis, the abdomen pendulous the curved lower limbs held apart and usually with one advanced in front of the other and both with knees slightly bent the ankles overhung by the legs and the toes turned out The enlarged cranium, square looking and bossed may add distinctness to these characteristics and they are completed in the slow and awkward gait of the patients" (Paget)

Up to the present time there is no thoroughly satisfactory explanation of the condition necessary to produce the lesions of osteitis deformans The disease does not seem to be hereditary or except in rare cases to run in families General arterial sclerosis is constantly present but this is probably an associated condition as one would expect to find arterial

*Manuscript submitted for publication Feb 28 1912

thickening at the time of life at which this disease manifests itself No definite connection is traceable between this disease and syphilis, though some of the recent French observers, because of improvement as the result of mixed treatment have considered that the disease is a manifestation of a parasuetic condition Gout, rheumatism and nerve lesions have been suggested as possible etiological factors but as yet nothing definite has been shown as confirmatory evidence It seems to us that the lengthening which accompanies the bowing and thickening of the affected bones, noted by Paget and quite marked in our own case, is a very suggestive fact, likewise the bulging of the skull The bowing, too, might well be accounted for as an active process as well as, or rather than, a passive giving way to the weight of the body since the bowing is always well marked in those bones which are fixed at both ends by muscles and ligamentous attachments, e g, the clavicle, radius and tibia, the accompanying bone (fibula or ulna) acting as the string to the bow

An interesting fact noted by Paget himself, and more recently by later writers is the intimate relation between osteitis deformans and the formation of malignant tumors Of eight cases traced to the end, five died with cancer or sarcoma "A remarkable proportion, suggesting careful inquiry"

The importance of the progressive step-like changes in the bones from apparently simple process to one of diffuse malignancy, occurring as they did in our patient while under observation in the hospital, demands for it the place it deserves in the medical literature on this subject

Before proceeding with the history, we wish to thank Dr C F Martin in whose service this case was kept under observation and under whose direction the clinical investigations were conducted

CASE HISTORY

D C Y male aged 56 goldsmith, born in Montreal was admitted to the Victoria Hospital Nov 15 1910 complaining of "bandy legs" and "rheumatism in the bones"

Family history negative Father and mother died at an advanced age from natural causes Three brothers and sisters alive and well (No bone disease in the family)

Past History—Has always lived in Montreal, married thirty years wife and children alive and well Save for chronic constipation and a "moist eczema" about the right ankle both of which he has had for several years, he has never had a day's illness that he can remember Habits regular (No venereal history)

Present Illness—This dates back six years, when, from no assigned cause, he begun to be subject to aching pains in the legs more particularly in the left and in the thighs The pain appeared deep seated in the bone, and, though not constant or very severe, seemed to bother him considerably, especially after walking During the following year the pain continued off and on and was sometimes accompanied by cramp-like pains in the calf muscles but at no time severe enough to necessitate his leaving off work or seeking medical advice He treated himself with local applications of liniment, and, except for his 'rheumatism' enjoyed perfect health

After about a year he noticed he was becoming "stiff" his limbs less agile and serviceable, and that his shins, especially the left were becoming misshapen Gradually his legs began to bow and, as he expressed himself he became so crooked in the legs that his family and friends frequently joked him about his bandy legs and rocking gait

About one year ago he began to have similar aching pains in the bones and muscles of the right forearm, and within a few months the radii began to bow similar to the leg bones About the same time he noticed his right collar bone becoming larger and more prominent

Though the use of his right arm aggravated the pain considerably he kept at work until two months prior to this report, when the pain extended up the arm and into the shoulder joint and he had to give up and go home since he had done no work

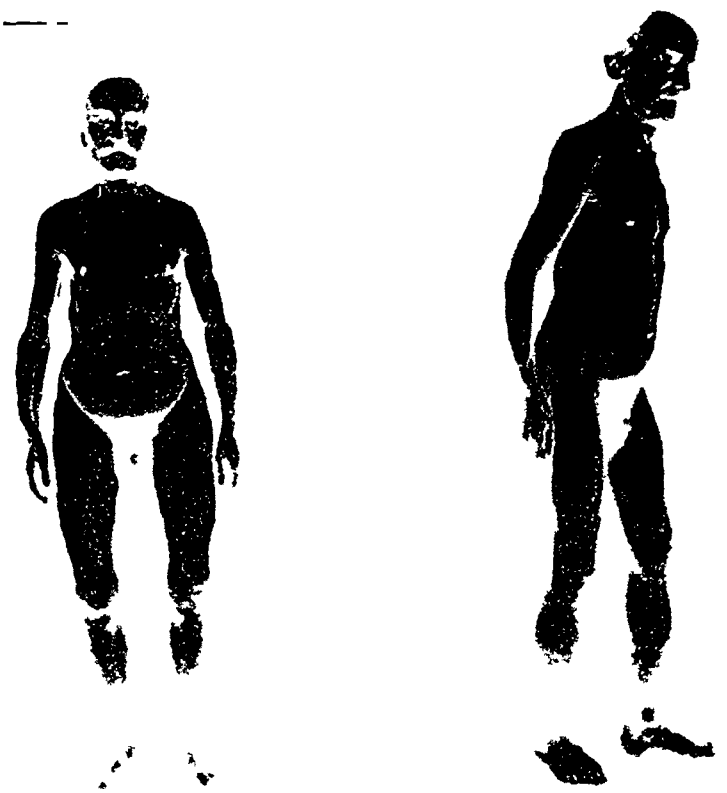

Fig 1—Front view of patient showing the bowing of the legs and the absence of a mass on the clavicle

Fig 2—Side view of patient, showing the marked thickening of the tibiæ

For the previous three years his head had been gradually increasing in size In buying his hats he noticed that each time he had to get a larger size than before and whereas previously he used to wear size 6⅞ his last hat was 7¼ His height too diminished considerably and—though he could not say definitely—he thought he was fully 2 or 3 inches shorter than before

Throughout his general health continued good He lost no weight and there have been no mental symptoms Appetite and digestion had been good

Physical Examination—Patient was a man of small stature cheerful and bright mentally and appeared perfectly well

The eyes ears throat and neck were normal the chest was narrow and long expansion limited lungs apparently normal The cardiovascular system except for slight general arterial thickening was normal Blood film and cell count

normal The gastrointestinal system, save that the abdomen was pendulous in its lower half, was normal

The nervous and genitourinary systems were also normal

Locomotor and Integumentory Systems The gait was peculiar and not unlike the stiff rocking gait of a pacing horse The body when in repose was considerably stooped (in the accompanying photograph (Fig 1) he is straightened up to the fullest extent) and the movement of the spine was stiff and limited The legs were bowed and the bones enlarged and misshapen The tibiæ especially the left were markedly enlarged and felt rough and tuberous in the middle third There was actual lengthening of the tibiæ with extreme bowing forward so that the legs appeared to "overhang" the ankles The femora were bowed outward and forward and felt rough and large (no tenderness over these bones, knee and ankle joints free) Full movement of the right arm, especially abduction, was slightly limited because of pain in the right shoulder joint The shaft, and

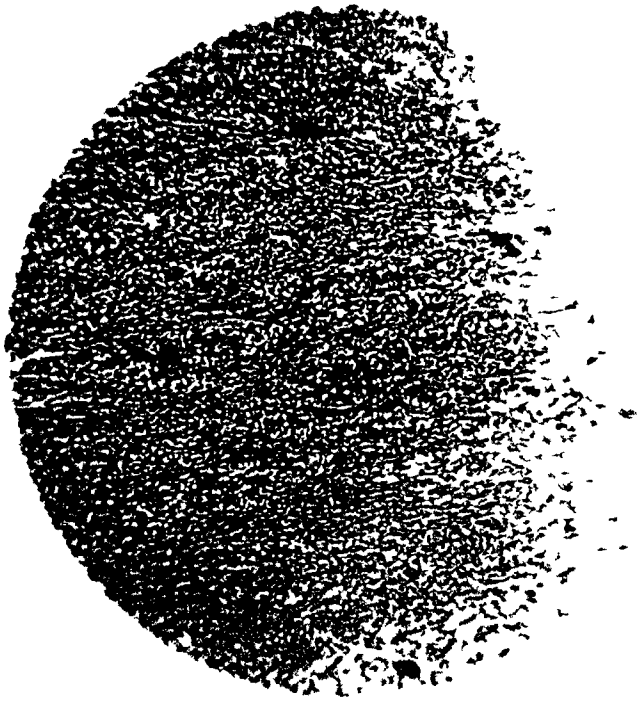

Fig 3.—Micro photograph of section of tumor of radius previous to amputation of arm Low power view The specimen shows delicate bands of fibrous tissue between which lie lines of polymorphous cells The tissue is rather loose in texture

especially the head, of the humerus was considerably larger than the left The right radius showed marked bowing and was slightly enlarged, but felt smooth The right clavicle was enlarged, bowed forward and appeared more circular than the left The cranium was large for the size of the body and was especially prominent or bulging in the frontal and occipital regions There was no sign of exostoses about the skull

Subsequent Events.—Patient felt about as usual until Dec 15, 1910, during which time metabolism experiments were carried out and serial skiagraphs taken, when he began to complain of constant pains in the right shoulder and forearm The slight fulness about the upper arm and shoulder developed into a diffuse,

firm swelling obliterating the natural landmarks of the shoulder and the movement of this joint became limited because of pain and fixation About the same time a fusiform swelling appeared in the middle of the right forearm chiefly in relation to the radius This swelling, unlike that about the shoulder felt soft elastic and was very tender It seemed certain that a firm sarcomatous growth was developing in the radius and head of the humerus (A section was taken from the tumor mass confirming the diagnosis) (Fig 3) Both swellings advanced rapidly and the pain became extreme, keeping him awake at night About Jan 5, 1911, spontaneous but apparently incomplete fracture of the radius occurred In order to relieve him from a useless and painful encumbrance it was thought best to remove the arm The subscapular amputation was done and the arm together with three-fourths of the clavicle, were removed Feb 22 1911

He made a good recovery from the operation and felt well and free from pain The wound healed quickly, but within three weeks he developed in rapid succession three small hemispherical nodules on the frontal and parietal bones and lastly behind the right eye and on the stump of the clavicle About this time

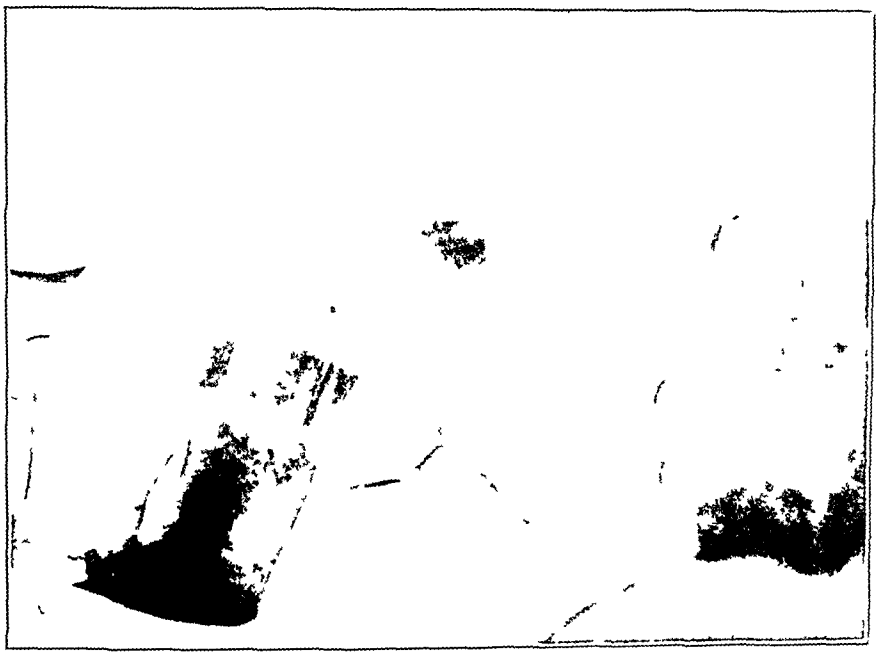

Fig 1—Photograph showing the condition of the legs shortly before the patient's death

he began to show signs of cerebral involvement—left facial paralysis, ankle clonus, double Babinski and Oppenheim reflexes From this time on he began to go down hill rapidly Strength failed and emaciation became extreme Toward the end he developed an acute otitis media and for the first time ran an irregular temperature and complained of headaches He became delirious and died May 15 1911

METABOLISM EXPERIMENT

Technic—The patient was put on regular diet during the experiment consisting of a given weight of shredded wheat biscuit milk soda biscuit butter tea and sugar for breakfast and for dinner in addition to the above chicken or fish and potatoes, for supper the breakfast fare was repeated (A duplicate quantity of each foodstuff was set aside for analysis) At the beginning gr x (0 6) of carmin was given, and with the appearance of red stools all excreta was collected At the end of the period carmin gr x (0 6) was again given and with the appearance of the characteristic stool the experiment ceased

The experiment began with breakfast on Dec 5, 1910, and continued five days The weight of the subject at the beginning was 100 pounds and at the end 99 pounds

TABLE SHOWING THE RESULT OF METAPOLISM EXPERIMENT IN THE AUTHOR'S CASE *

	Nitrogen Gm	P_2O_5 Gm	CaO Gm	MgO Gm
Total outgo				
Urine	46 11856	12 74335	10 33625	2 19932
Feces	3 6			
Total intake	38 97304	9 8578	7 13027	1 61920
Av daily intake	7 7946	1 9715		
Av daily outgo	9 9137	2 54867		
Av daily loss	2 1491	0 57717	0 64119	0 116
Total loss			3 20598	0 58012

* Thanks are due Dr A A Bruere, who was kind enough to conduct the analyses in this experiment

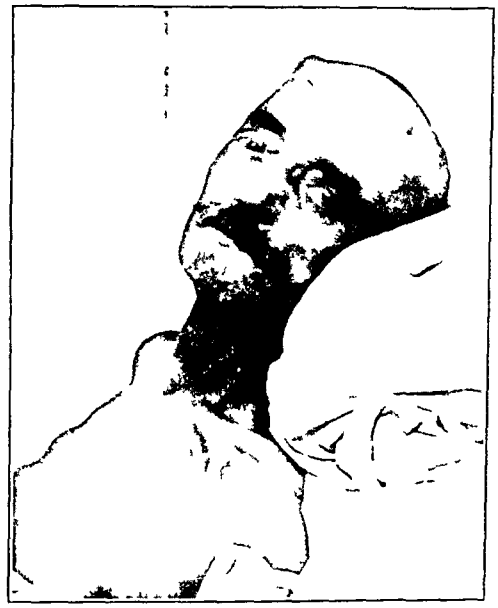

Fig 5 —Photograph showing the exophthalmus and the mass over the clavicle, shortly before death

PART II BY F A C SCRIMGER

THE PATHOLOGICAL CHANGES IN THE RIGHT UPPER EXTREMITY

There were two tumors, one a smooth, slightly irregular mass situated at about the middle of the radius, the other an enlargement of the head of the humerus Corresponding to these growths, abnormal movements of the bone gave evidence of spontaneous fracture having occurred The limb was sawn through longitudinally from end to end by means of a band saw in order to study the gross changes in the different parts of the limb

Ulna Naked eye appearances of the longitudinal sections of the bones — The ulna, bones of the wrist and hand showed practically no naked eye changes Throughout the shaft of the ulna there was clearly defined compact bone, and a wide spaced network of cancellous bone at either extremity, with a well developed fat containing (medullary) cavity The small bones of the carpus, metacarpus and phalanges appeared to be normal

Scapula The scapula showed no obvious change

Clavicle The clavicle showed a uniform ivory like cut surface, with complete absence of differentiation between compact bone, spongy bone or medulla The cut surface was of a gray color

Humerus The length of the humerus was not increased, but there was a slight anterior bowing There was a thickening in the middle portion of the shaft at about the level of the insertion of the deltoid At the level of the surgical neck, 7 5 cm below the highest point of the articular cartilage, there was an irregularly transverse spontaneous fracture A large solid mass of new growth measuring 9 5 cm in its greatest transverse diameter, and 9 cm in its greatest longitudinal diameter, surrounded the head of the bone above this point It was intimately blended with the head of the bone so that the outline of the shaft and tuberosities was lost in that of the tumor The outer portions of the growth were firm in consistence and contained no calcareous deposit, but the central portions were calcifying A similar change appeared toward the head of the bone, which had the ordinary consistence of bone There were softened areas in the central parts of the head, but the portions close to the articular surface were of ivory-like consistence and color Below the line of fracture the whole shaft had become altered in appearance It was a little thickened, measuring 3 cm at its widest diameter There was an entire loss of differentiation between compact and spongy bone, owing to uniform replacement (except for a narrow channel representing the medullary space) by bone of a different character, having a rather coarsely

Fig 6—Low power view of radius showing the porous character of the bone and the replacement of marrow by fibrous tissue

granular surface and a gravish color The marrow cavity measured only 25 to 5 cm in width but was not present along the whole length of the bone

Radius Occupying the middle of the shaft of the radius was a large well-defined tumor 6 by 4 5 cm, separated from the shaft of the bone by two lines of fracture, 4 cm apart Enclosed in its center was a portion of partially destroyed shaft The medullary canal was greatly reduced and was partly filled in by a soft growth of sarcomatous appearance which was continuous with the main mass The tumor tissue was soft and elastic, the remnant of the shaft of the radius within the center of the tumor being the only calcified portion in the mass Above and below the tumor, the whole bone presented the same appearance as has been described for the non tumor portions of the humerus namely absence of differentiation, reduction of narrow cavity replacement of both by new bone of ivory like character

Microscopical Characters—Upper end of ulna The compact bone was regular and showed well marked Haversian systems Towards the periosteum bone cells were scanty and the bone was dense in structure while passing inwards the bone cells were more numerous and in the cancellous portion the bone trabecu-

læ were slender far apart and covered by a single row of osteoblastic cells The intertrabecular spaces were large, irregular and filled by a delicate fatty areolar tissue containing only a minimal amount of normal bone marrow cells Large capillaries were seen There were no giant cells and no evidence of bone destruction or unusual osteoblastic activity

Carpus Metacarpus and Scapula The carpal and metacarpal bones and portions of the scapula presented a similar appearance, the bone trabeculæ being thin and the intertrabecular spaces large The latter contained only fat Some of the capillaries showed thickening of the adventitia Osteoclasts were few in number The condition was one of slight osteoporosis

Fig 7 —Section from radius near the tumor showing the reticulum of new bone, many of the cells being separated from one another by a circumferential deposit of bony substance High power view

Radius The periosteum was of usual thickness The bone immediately beneath it was spongy the outermost trabeculæ being all arranged parallel to the long axis of the bone The compact layer was thus reduced to the thickness of one trabecula This layer was imperfect and irregular To the inner side, the trabeculæ were quite irregularly arranged and formed the framework of the newly developed bony layers The latter were not only smaller but more numerous than those of normal bone, and were very irregular in outline and density The individual trabeculæ presented a worm eaten appearance from the pitting by osteoclasts (Fig 6) The intertrabecular tissue was fibrous and rather poor in cells, though toward the periphery spindle shaped cellular elements were more

numerous Bone marrow tissue was absent, except for a narrow stratum in the central portion of the bone Multinuclear giant cells occurred in varying number They were always closely applied to the bony framework and lay in pits thereon sometimes in groups It was in such places that the irregularity of the bony trabeculæ was very evident The spaces remaining between them were frequently no larger than the bulk of a giant cell In some portions of the tissue the connective tissue consisted of conspicuous numbers of fuchsinophil fibers Surrounding the larger trabeculæ there were usually single files of osteoclasts, cells with a moderate amount of cytoplasm, deeply staining nucleus and tending to elongate at their free surface into the fuchsinophil fibrillæ already referred to

Radius Above Tumor This tissue showed many of the characters of the preceding, but nearer to the tumor itself, the intertrabecular spaces were full of irregular patches of osteoid substance and the edges of the original trabeculæ were deeply and widely scalloped, indicative of active destruction They were replaced here and there by irregular plates of young bone The trabeculæ were massive

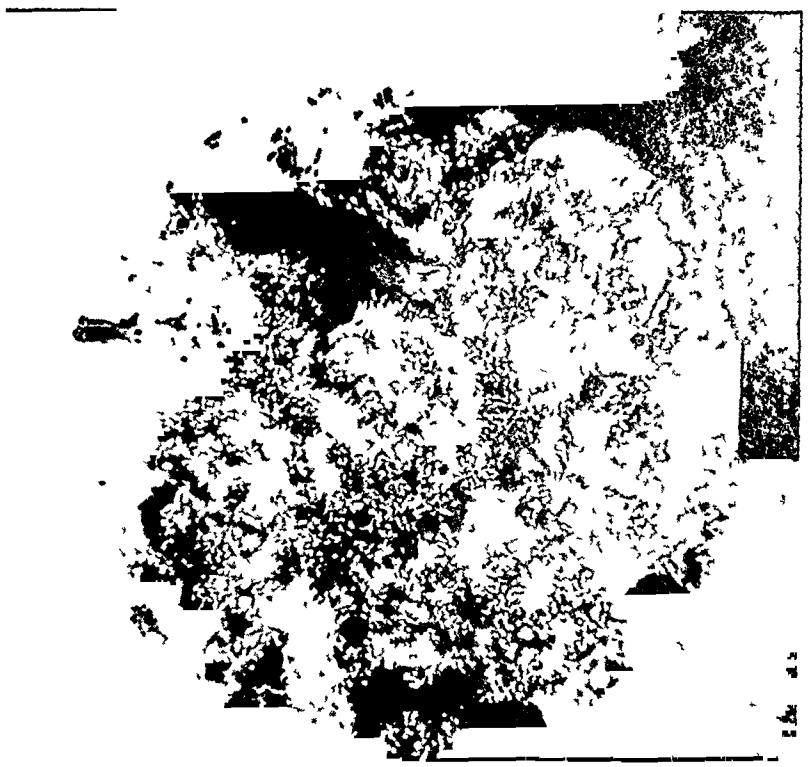

Fig 8—Tissue from the head of the humerus, magnified 200 diameters, showing the original trabeculæ of bones as thick bands widely separated from one another The intervening tissue is occupied by a fine irregular network of new osteoid tissue

Shaft of Humerus Well Away from the Tumor Therein The structure was similar to that in the radius away from the tumor The medullary canal showed a few relics of marrow tissue The bone structure presented irregular spaces containing fibrous tissue through which ran many distended blood vessels enclosed in a spindle celled tissue A few relics of fatty tissue occurred here and there within these intertrabecular spaces Passing up towards the tumor the cellular tissue became more dense and abundant and white fibrous tissue appeared in increasing amount Varying quantities of hyaline matter could also be seen to be replaced, further away by a dense hyaline matrix in which lay the individual cells The structure here recalled that of a honeycomb and was very character-

istic (Fig 7) The appearance of calcification and ossification in the trabecular network resulted in the formation of extremely fine meshed bony material, which lay within the widened intertrabecular spaces of the original bone trabeculæ (Fig 8) The latter were thickened here and there, though as a rule they were becoming attenuated from absorption The stability of the bone, otherwise endangered by this process, was maintained by the ossification of these new deposits Where the tissue was seen in longitudinal section the appearance was slightly different, owing to the fact that the strands of osteoid tissue ran in long slender lines which interlaced only at long intervals (Fig 9) Then walled blood vessels were seen passing through the tissue in abundance

The Tumor in the Humerus This showed a very characteristic appearance, and though detailed description might be enlarged on the essential feature of the tissue was its close resemblance to that of many another ossifying sarcoma There were here no relics whatever of the original bone There were zones of

Fig 9 —Longitudinal section of tissue in humerus showing the long delicate spicules of new bone tailing off into a loose spindle celled tissue which has sarcomatous characters Magnified 200 diameters

intense vascularity alternating with zones of closely packed cells of the typical short spindle or oat shape, and alternating also with zones in which but few cells were present at all Such regions as the latter showed a mucinous looking material with delicate stellate cells like those seen in invertebrate cartilage Some of these cellular districts showed no intercellular hyaline substance, others presented the typical honeycombed appearance and others showed a dense anastomosing network of hyaline matter in which were a few cells There was here distinct resemblance to the abnormal closely meshed reticulation of osteoid tissue formed by osteosarcomas

The different parts of the humerus about the tumor show similar features though varying considerably in the number of cells which are present and in the relative number of osteoid trabeculæ

Passing away from the tumor the characteristic interlacing of osteoid trabeculæ with normal trabeculæ is seen, the new bone blending with the old and the new trabeculæ resting on the old like distorted columns on a base This arrangement is also a common finding at the edge of an osteosarcoma

Further away again the tissue acquires the loose appearance (Figs 10 and 11) which was described in the case of the ulna Some foci in the head of the humerus show advancing tumor with very little interstitial deposit so that the stroma has a gelatinous appearance

Clavicle The clavicle shows very irregular bone formation with numerous giant cells and a loose intertrabecular tissue which is exactly identical with that seen in the lower end of the radius This is a condition of osteosclerosis of slight degree replacing osteoporosis, but in some sections of this bone there is development of spindle celled tissue which is exactly like the sarcomatous areas of the other bones, minus ossification

Fig 10—Section from shaft of humerus well away from tumor showing the wide separation of the original bony trabeculæ and their rounded contour, the intermediate tissue is loosely fibrous The appearance here is very like that of osteomalacic bone Magnified 200 diameters

Summarizing the appearances, it is evident that the sclerosis of the bone in the densest areas is entirely due to the ossification of the spindle celled tissue which has arisen in place of the original marrow of the bones, and in this respect cause the specimen to have characters which are completely in accordance with those of primary osteosarcomas of local or limited distribution The essence of the present case consists in the generalization throughout the bones of osteoporotic and osteosclerotic changes

PART III BY O C GRUNER

ABRIDGED AUTOPSY REPORT

The chief external findings were marked emaciation nodules on the skull and inner end of right clavicle and bone deformities as mentioned in the clinical

report The mass in the clavicle was continuous with a tumor occupying the apex of the right lung The skull cap was ivory like on section and the tumor seen externally communicated by slender pedicles with flattened masses on the inner surface of the skull Tiny chalky white masses followed the line of the longitudinal sinus The tip of the right frontal lobe was intimately connected with a large mass of tumor (about the size of that at the end of the clavicle) which passed through into the right orbit, enveloping the eyeball, coming to the surface as a nodule under the upper lid close to the eyebrow, half way between the two canthi The pituitary gland was very small and rested on only a shell of bone separating it from a large sphenoidal sinus

The brain itself was normal

Fig 11 —Section from shaft of humerus still further away from the tumor than Fig 10 This shows the erosion of the original trabeculæ by numerous osteoclasts Magnified 700 diameters

In the chest, the pleural surfaces were found to be occupied by discrete nodules of tumor, around the edges of which were loose adhesions Where adhesions did not occur, pools of fluid had collected between the two layers of the pleura The lung substance was riddled with small tumors, which varied in size from a pin's head to 2 5 cm in diameter, some of them were pink in color and some were chalky white The apex of the lung was shrunken and hard, owing to the presence of a mass of new growth measuring 5 by 4 cm , continuous with that in the head of the clavicle The cut surface of the tumor nodules was gray, finely mottled with injected blood vessels The air passages were normal

The heart showed some deposits of fatty atheroma in the valves The thyroid was small The abdominal viscera presented no feature of special interest, save that the adrenals were small

HISTOLOGICAL STUDY

Bone-Marrow A differential count made from the smears of the bone-marrow of the sternum yielded the following results Large lymphocytes 9 2 per cent , small lymphoid cells 2 7, lymphoidocytes 83 3, neutrophil myelocytes 3 3, eosinophil myelocytes 1 5 per cent

Tumor of Skull (External) The central parts of the tissue were very hyaline and the relics of delicate spindle cells which occurred were widely separated by the dead material Toward the edge, within the well-defined fibrous envelope, were better preserved cells, amongst which were plasma and mast cells (Fig 12) The tissue resembled that in the lung nodules save for the greater degree of necrotic change

Tumor of Skull (Internal) This was very similar to the orbital tumor

Orbital Tumor The orbital tumor consisted of exceedingly well formed bundles of spindle cells whose nuclei stained deeply, were elongated, oval in shape and had an oxyphil cytoplasm They tended to form wavy bundles Occasional

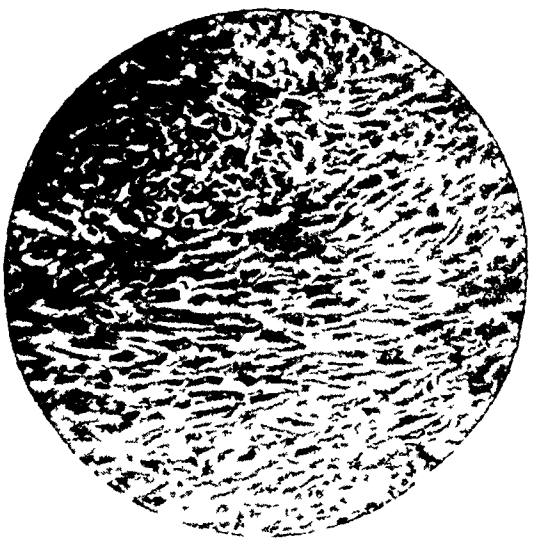

Fig 12 —Section from the tumor in the skull Magnified 400 diameters This specimen shows the individual cells separated widely from each other, and a delicate deposit of new bone appearing around each

areas occurred in which there was only dead material The edges of such areas were drawn out into filamentous bands which interwove with the long delicate bodies of the living sarcoma cells In other areas the intercellular substance tended to accumulate around individual tumor cells as if preparing to pass over into osteoid tissue

Thyroid There was marked increase of the fibrous tissue with separation of the glandular acini

Lungs The nodules were similar in structure to the tumors already described Otherwise there was no feature of special interest

The other viscera showed no microscopic changes worthy of special note

PART IV BY O C GRUNER AND F A C SCRIMGER

A review of the literature on the subject of osteitis deformans is not called for in view of the frequency with which different authors have undertaken the same Highee and Ellis estimate that there have been

158 cases reported to January, 1911 Most of these reports are purely clinical and careful description of the changes taking place in the bones is seldom available There are only fourteen cases in this series in which there has been an associated tumor growth These cases all occurred before 1902 The writers conclude that there is no close relation between the changes found in osteitis deformans and the development of malignant disease This view seems incorrect in the light of the present case, as will be presently shown

Paget described and figured the disappearance of the compact bone the encroachment on the medullary canal by the relatively dense new bone, the small irregular trabeculæ surrounded by osteoblasts, the fibrous connective tissue filling the intertrabecular spaces, and, finally, the tumor which he called a "cancer' which was a typical spindle-celled sarcoma Five out of the eight cases which he reported were associated with tumor formation These main features are common to all the cases in the literature in which histological examination was made

There are no etiological indications to be made out either in the personal or family history of the patient, but there were slight changes in some of the ductless glands The thyroid adrenals, prostate, testes, and especially the pituitary body were atrophic

The interpretation of the changes met with in the tissues examined in the present case becomes easy by considering the course of the illness The clinical notes state that aching pains occurred in the limbs for six years, that the deformity of the limbs had become conspicuous for four years Enlargement of the radius and head of humerus were only noticed on admission to the hospital and they rapidly increased in size until the time of death

The changes in the bones at situations most distant from the tumor masses are those of osteoporosis while close to the periphery of the growths the changes were those of osteosclerosis In only three bones was there a continuous transition from osteosclerotic bone to the cellular sarcomatous tissue The masses in the skull were evidently secondary tumors and were quite sharply marked off from the cranial bones The order in which these phenomena appear is at once seen to be the same as that of the clinical symptoms which are recorded The osteoporosis would be marked by osteocopic pains spread over a long period of time, the osteosclerosis which is histologically implanted on the other lesion would cause similar symptoms, but, following as it did on the other change, would not prevent the bowing of the limbs characteristic of osteomalacia The sarcoma formation, finally, was so late that the patient himself had never noticed it till it was pointed out to him The cranial nodules were not present at the time of admission

The secondary deposits had a peculiar distribution They occurred over the pleural surface and in the meninges The scattered lesion of the lungs without dissemination in other viscera suggests a lymphatic mode of transport There was entire freedom from secondary deposits of the organs below the diaphragm

The chief question at issue, therefore is as to whether the cellular tissue occupying the osteoporous bone was primarily sarcomatous in nature or whether the sarcoma formation was a secondary change In other words, was the formation of tumors an accident or was it the inevitable result of the morbid process?

The microscopic changes seen in the portions of bone away from the tumors are not essentially different from those seen in any rapidly growing bone, or in the process of formation of callus The activity of the cell-elements is merely an exaggeration of the usual methods of absorption with subsequent replacement of bone tissue Where there is no osteosclerosis, the changes are so like those typical of osteomalacia that some sections could not be distinguished from sections of purely osteomalacic bone Where there is osteosclerosis, again, the changes are hardly distinguishable from those seen in a syphilitic osteosclerosis The formation of dense bone may be looked on as nothing more than a reparative process called forth to counteract the production of deformity To this extent the changes have no semblance to neoplastic transformation The only possible argument in favor of the latter supposition is that the bone-forming cells are smaller and more numerous than osteoclasts in regenerating bone, and that the bone trabeculæ formed are quite atypical in form arrangement and size

The essential difference between the sarcomatous portions and the adjoining osteosclerotic portions lies in the unrestrained multiplication of the tumor cells, which here fail to exhibit the slightest tendency to deposit bony matter around them The limitless growth of these cells further produces a macroscopic tumor, whereas no conspicuous or localized enlargement occurs anywhere else This again suggests that the tumor formation was superadded on an already altered osseous tissue

The evidence so far submitted points to the view that the sarcoma formation was not the inevitable result of the disease from which the patient ultimately died The strongest argument lies in the fact that six years elapsed before neoplasms appeared The fact that no sarcoma developed in the altered tibia, femur, and skull would be difficult to explain on the supposition that the disease was a latent sarcoma from the outset

The alternative view is that the patient developed osteomalacia with subsequent hyperplasia of the bone-forming elements of the connective tissue of the bone marrow that these changes persisted for some years and that under the influence of some other stimulus (or consequent on

the removal of some inhibitory stimulus) sarcoma suddenly and rapidly developed in certain regions It is interesting to note in this connection that the pituitary body, when the subject of hypertrophy, is associated with overgrowth of bone, so that its marked atrophy in the present case might have led to the opposite effect and account for the failure of the "tumor cells in some situations to secrete bone The inevitable result of such failure would be ability of these cells to multiply vigorously and without restraint

In one sense this view could be paraphrased into a statement that the spindle cells of the sarcoma and the fibroblastic cells of the bone marrow are at opposite ends of one series — this series, beginning with the overgrowth of the fibroblastic element of the bone marrow, destroying or replacing the marrow cells, and ending with the development of a malignant tumor The multiplication might either be the result of an initial stimulus or might require a constant irritant such as might be furnished by the overgrowing cells themselves or, finally, it might consist of the removal through atrophy of some influence exerted by the pituitary body or other ductless glands

THE PROGNOSIS OF ALBUMINURIA WITH OR WITHOUT CASTS

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The question as to the significance of albumin and casts in the urine of apparently healthy men is a much-mooted one, the answering of which, from a clinical point of view, has been difficult on account of the scarcity of cases in hospital and private work, and the impossibility of following them through a number of years During the late nineties several of the large New York insurance companies began to insure men with this condition, and since then records of a large number of such cases have accumulated It was through the courtesy of one of these companies that we were given an opportunity to investigate the above-mentioned problem under very promising conditions

The material placed at our disposal consisted of 396 men, residents of New York City, who were insured during 1900-1901 As far as an ordinary physical examination could determine, they were normal at that time except for the presence in the urine of serum albumin with or without casts Only office specimens of the urine were secured, but albumin was found on at least two occasions in one-half of the cases This was before the day of blood-pressure observations by examiners for insurance companies

The preliminary examination of the urine was done by the examining physician, using the ordinary heat and nitric acid test for albumin His findings were always confirmed by an experienced clinical pathologist, who also made all the microscopical examinations according to the following routine Fifteen cubic centimeters of the specimen were centrifuged for five minutes and the entire sediment then examined with the aid of a movable stage All the specimens were examined within eighteen hours of the time they were passed, and many a few hours after passing

Following their examination during 1900-1901 by the insurance company, these 396 men were divided into three groups The first, numbering 115, showed albuminuria without tube-casts (no cases of pyuria were included in this group), the second group, numbering 203 showed albuminuria and a few hyaline casts, and the third group included fifty-three men showing albuminuria and a few granular casts

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*Read in the Section on Practice of Medicine of the American Medical Association at the Sixty-Third Annual Session held at Atlantic City June 1912

The incidence, by decades, of these three groups is of interest and we were able to estimate it fairly accurately with the help of statistics showing the age-distribution of all of the company's entrants during the past ten years The men showing albuminuria alone were five times more frequent before the twentieth year than after The albuminuria and hyaline-cast group showed approximately the same incidence in the second, third, fourth, and fifth decades The men with albuminuria and granular casts showed an increasing incidence in each decade, until,

TABLE 1.—EXAMINATION OF TWENTY MEN, TEN YEARS AFTER ALBUMIN HAD BEEN OBSERVED IN THEIR URINES

	1900-1901		1911	
Age	Serum Albumin on Uranalysis†	Examin Heart	Systolic Blood-Pressure	Uranalysis†
*17	+	—	128	—
19	++	—	120	—
19	++	—	132	—
21	+	—	120	—
21	++	—	112	—
22‡	++	—	112	+, no casts
23	++	—	98	No albumin, 1 hyaline cast
*23	+	—	112	—
*24	+	Two, —	142-132	—
*26	++	Three, —	142-132-128	—
27	++	—	128	—
*27	++	—	116	+, few hyaline casts
*27	++	—	128	—
27	++	—	136	No albumin, 3 hyaline casts, 1 granular cast
*30‡	++	Two, —	140-132	Trace albumin, no casts
*30	++	—	124	—
*32	++	—	133	+, no casts
*33	++	—	126	—
*36	+	—	122	+, no casts
39	++	—	124	+, 1 hyaline cast

*Cases which had shown albumin on two or more examinations

†In this column, in this and the following charts, + indicates trace of serum albumin, small quantity, the sign — throughout means negative

‡In these cases traces of albumin have been repeatedly found since 1900

between 40 and 50 years, they were four times as frequent as between 20 and 30 years After 50 years of age so few men are insured, as compared with younger entrants, that statistics of later decades are of little value

The age-incidence in the albumin group and the granular-cast group is quite in accord with general experience The almost equal decade-

incidence of the hyaline-cast group was, however, unexpected, the usual assumption being an increasing frequency of this condition with advancing age

TABLE 2.—EXAMINATION OF THIRTY MEN TEN YEARS AFTER ALBUMIN AND A FEW HYALINE CASTS HAD BEEN OBSERVED IN THEIR URINES

1900-1901			1911	
Age	Uranalysis†	Exam Heart	Systolic Blood-Pressure	Uranalysis†
18	++	—	130	+, no casts
18	+	—	130	—
*22	+	Two exams —	146-132	—
*23	+	—	131	—
*23	+	—	122	—
25	+	—	132	—
*25	+	—	122	—
*25	++	—	130	—
*27	+	—	129	—
28	++	—	134	No albumin, a few hyaline casts
*30	+	—	128	+, few hyaline casts
30	+	—	142	—
*32	+	—	130	—
32	+	—	128	+, few hyaline casts
33	+	—	130	—
34	+	—	134	—
*34‡	++	Two —	160-136	+, hyaline casts
36	+	—	132	No albumin, a few hyaline casts
36	+	—	142	+, no casts
*36	+	Three —	140-128-136	+, no casts
*37‡	+	Apex normal position and heaving, otherwise neg two exams	140-136	+, few hyaline casts
37	+	—	143	—
37§	+	Apex 4 in from midline heaving	198	+, few hyaline casts
38	+	—	102	—
*39	+	—	129	1 per cent glucose
*39	+	—	128	+, few hyaline casts
*39	+	—	138	+, few hyaline casts
*40	+	—	136	—
*43	+	Two —	138-130	—
47	+	—	124	—

*Cases which had shown albumin and casts on two or more examinations The microscopic examination was similar in all these cases, a few hyaline casts being found

‡Doubtful cases

§A case of interstitial nephritis

During the summer of 1911, seventy of the original 396 men were visited and examined, from ten to eleven years thus having elapsed since

their first examination The history was first discussed, then the heart was examined and the systolic blood-pressure taken For the latter a Faught instrument with wide cuff was used, the subject being each time in a sitting posture If the pressure was above normal another reading was made several days or weeks later, and at the same time the heart was reexamined Also an eight-hour specimen of urine was collected (in most

TABLE 3.—EXAMINATION OF TWENTY MEN TEN YEARS AFTER ALBUMIN AND GRANULAR CASTS HAD BEEN OBSERVED IN THEIR URINES

1900-1901			1911	
Age	Uranalysis†	Exam Heart	Systolic Blood-Pressure	Uranalysis†
21	+	—	130	No albumin or casts, 6 per cent glucose
23	+	—	132	—
26	++	—	136	+, hyaline casts
*26	++	—	122	—
*26	+	—	132	—
27	++	—	98	—
29‡	+	Apex 4 in from midline heaving, 2 exams	137-136	—
*31	+	—	128	—
33§	+	Aortic 2d, accentuated, otherwise neg	150 144	No albumin, few hyaline casts
34	+	—	128	—
34	+	—	136	—
*35	+	—	132	+, hyaline casts numerous
37	+	—	129	+, granular casts
39§	+	Aortic 2nd accentuated, otherwise neg	170	+, hyaline casts
*41‡	+	Apex 5th from midline, heaving	158	+, many pus-cells
43	++	—	128	+, hyaline casts
43§	+	Two —	150 142	+, no casts
43§	+	—	162	+, no casts, 5 per cent glucose
*47	++	—	134	+, granular casts
47§	++	—	170	+, hyaline casts

‡Cases of interstitial nephritis
§Doubtful cases
The microscopic examination was similar in all these cases, a few granular casts being found

instances night urine) and examined the next day Examination of the eyegrounds in these men was not feasible, otherwise we might have had fewer cases in which the diagnosis was doubtful

Twenty of the men we visited had shown albumin, but no casts, in 1900-1901 Our results in this group are summarized in Table 1

None of these twenty men now has interstitial nephritis, as far as we can judge from the condition of the heart, the blood-pressure and the examination of the urine Twelve are, apparently, normal as regards heart and kidneys In eight we find the same condition of the urine as was found ten years ago, four now showing in addition tube-casts

The absence of interstitial nephritis in any member of this group after ten years had elapsed was most interesting

Thirty of the men we visited had shown albumin and a few hyaline casts in 1900-1901 Our results are summarized in Table 2

One of these thirty men now has interstitial nephritis and two are doubtful cases Five men show a slightly raised blood-pressure, not marked enough, however, to justify any suspicions of nephritis, considering that ten years has elapsed since the first appearance of trouble Eighteen men are, apparently, normal as regards heart and kidneys Nine show the same condition of the urine that they did in 1900

Twenty of the men we visited had shown albumin and a few granular casts in 1900-1901 Table 3 summarizes our results

Of these twenty men, two now have interstitial nephritis and in five the diagnosis is doubtful Eight are apparently normal as regards heart and kidneys

Considering the entire series of seventy men, at the present time thirty-eight are, apparently, free from cardiac or renal disease Three have chronic interstitial nephritis and seven possibly have it Two have diabetes Twenty-two still show much the same urinary condition as they did ten years ago, but with no circulatory changes

Of the ten men who now have, or possibly have, nephritis, but one was under 30 years of age at the time trouble was first discovered

THE MORTALITY IN THE ORIGINAL GROUP OF THREE HUNDRED AND NINETY-SIX MEN

We found that twenty-five of these men had died since their examination in 1900-1901 The causes and dates of death are enumerated below

ALBUMINURIA GROUP

	Cause of Death	Year of Death
1	Pulmonary tuberculosis, tuberculous meningitis	1902
2	Typhoid fever, perforated ulcer, operation	1903
3	Pulmonary tuberculosis	1904
4	Illuminating-gas poisoning	1904

ALBUMINURIA AND HYALINE CAST GROUP

1	Appendicitis	1902
2	Fibroid phthisis, gastro intestinal tuberculosis	1903
3	Phenol (carbolic acid) poisoning	1904
4	Pulmonary tuberculosis	1904
5	Rheumatism, malarial fever heart failure	1905
6	Cirrhosis of liver	1907

7	Pulmonary tuberculosis, brain abscess	1910
8	Lobar pneumonia	1910
9	Syphilis, gumma of brain	1909
10	Pulmonary tuberculosis	1910
11	Pulmonary tuberculosis	1909
12	Unknown	1910
13	Heart failure after drinking bout	1903

ALBUMINURIA AND GRANULAR CAST GROUP

1	Appendicitis	1902
2	Cancer of stomach	1907
3	Valvular disease of heart, Bright's disease	1909
4	Pulmonary tuberculosis	1907
5	Chronic Bright's disease, cardiac hypertrophy	1907
6	Diabetes, coma	1910
7	Chronic Bright's disease, uremia	1910
8	Lobar pneumonia	1907

This mortality is decidedly high If these 396 men had been standard risks, that is if they had been free from albumin, in addition to being otherwise normal, there would have been *sixteen* deaths, instead of *twenty-five,* at the end of ten years This excessive mortality represents the usual experience of insurance companies in the general group of albuminurias, with or without casts A number of years ago the medical director of a large insurance company gave us the following statistics, calculated from the records of at least two companies

Impairment	Approximate Yearly Mortality per 10,000 Lives*
1 Small amount of albumin and occasionally hyaline casts, otherwise first-class (This group is composed chiefly of simple albuminuria cases)	137
2 Small amount of albumin and casts, other than hyaline, otherwise first class	220

*Average mortality among sound lives being 100

The mortality is lowest among men showing albuminuria only, but even here it is greater than among healthy subjects

THE INDIVIDUAL CAUSES OF DEATH AMONG THE THREE HUNDRED AND NINETY-SIX MEN

Assuming that the diagnoses on the death certificates were correct, there were three deaths from nephritis and eight from pulmonary tuberculosis This is quite surprising, as we had anticipated that the chief cause of death would be renal or arterial disease

This mortality from nephritis was high, inasmuch as approximately but one death from this cause might have been expected among 396 normal men It will be noticed that the three deaths occurred in the granular-cast group Insurance statistics show that the mortality from renal and arterial disease in the general group of albuminurias, with or without casts, is about 250 per cent greater than among normal people They

also show that the lowest mortality from these causes occurs in the group of simple albuminurias, but how this mortality compares with that among sound subjects we cannot state We have no statistics on the mortality in the granular-cast group, but the present condition of the twenty men who showed granular casts in 1900 (seven probably having nephritis), makes it probable that this group has the highest death-rate from renal and arterial disease

The eight deaths from tuberculosis was a remarkably high mortality, for 396 normal men would have shown approximately but two deaths from this disease No less interesting was the fact that this mortality exceeds the mortality from nephritis It seemed as if our figures might have been a coincidence working with such a small number of cases, but records of some thousands of these subjects showed the death-rate from tuberculosis to be 100 per cent greater than among normal subjects So while our figures were unusually high, they indicated correctly the tendency of these people toward tuberculosis

The next step was to ascertain whether any one particular group of albuminurias showed this tuberculous tendency, or whether it was distributed equally among the three groups In our small series, two of the four deaths from tuberculosis occurred in the albuminuria group Statistics based on a study of 1,700 cases of simple albuminuria showed that the mortality from tuberculosis among these people was 275 per cent greater than among normal subjects, and also that it was much higher than in either the hyaline-cast or the granular-cast group

The relation between albuminuria and tuberculosis has not heretofore been considered other than a casual one, as far as we can ascertain. Von Noorden, in a recent article,[1] describes various forms of harmless albuminuria, and among them one which he calls a pretuberculous albuminuria He speaks of this as occurring during any stage of pulmonary tuberculosis and as being caused probably by action on the kidney-cells, of toxins of the tubercle bacillus He does not speak of it, however, as occurring in a pretuberculous stage, so the reason for the name pretuberculous albuminuria is not clear

Lawrason Brown[2] considers albuminuria as rare in incipient tuberculosis, it was found in 5 per cent of 1,214 cases of pulmonary tuberculosis in all stages, at the Adirondack Cottage Sanitarium Cornet[3] says that the urine is normal in the earliest stages of the disease

The absence of nephritis, shown in our twenty cases of simple albuminuria, after ten years had elapsed, and the low mortality in this group from renal and arterial disease indicate that it is exceptional for the albuminuria of young adults to be a symptom of incipient nephritis

1 Von Noorden Ueber Albuminurie, Ztschr f Urol , 1907, 1, 1017

2 Osler's Modern Medicine, III, 323

3 Cornet Die Tuberkulose, 1907, II, 634, Nothnagel's Specielle Pathologie und Therapie

On the other hand, the high mortality from tuberculosis in this group leads us to consider albuminuria, in the absence of other symptoms, rather as an evidence of a lowered bodily resistance, which is manifested in later years by the person's increased susceptibility to tuberculous infection

CONCLUSIONS

1 Renal albuminuria without casts is most frequently found in young adults It is exceptional for it to be a symptom of incipient nephritis It is rather to be regarded as an evidence of a generally lowered resistance which predisposes to tuberculous infection The mortality among these people is higher than among normal subjects

2 Cases of albuminuria with a few hyaline casts have no particular age-incidence The mortality in this group is also above normal

3 People with albuminuria and granular casts show a much higher mortality than normal people and a much greater tendency to renal and arterial disease than either of the preceding groups

4 Whatever the urinary findings, age is a factor in the prognosis of albuminuria, young people having the most favorable outlook as regards the possibility of an ultimate nephritis

We are greatly indebted to Dr Franklin C Wells for his courtesy in furnishing us with the material and records to do this work

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METABOLISM OF SCURVY IN AN ADULT

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I INTRODUCTION

This study was undertaken for two reasons First, we wished to determine whether it were possible to make an accurate study of the metabolism of a rational bed patient in the hospital ward available to us, without the assistance of a special nurse Second, to determine whether or not a study of the mineral exchange would yield any information of value concerning scurvy, a disease which may be eventually regarded as a disturbance of metabolism

Our first question can be answered in the affirmative If an intelligent ward nurse, an interested intern and the usual hospital facilities are available, a metabolic experiment such as the one described by us, is possible

The methods employed were for the most part tested on standard solutions and modified when necessary to meet experimental conditions and increase their accuracy

II LITERATURE

An exhaustive study of the Index Medicus and Surgeon General's Catalogue as well as the special *Centralblatter* for biochemistry, medicine and pediatrics, yielded little or no information of value Most of the literature on this subject deals with the much mooted etiological question but has no bearing on our paper Except for various contradictory statements by the older writers as to the commoner mineral and organic constituents of the urine, nothing of any moment could be found Garrod[1] in 1848 found that antiscorbutic articles of food were richer in potassium than ordinary food material and that the urine and blood of scurvy patients contained a diminished amount of potassium salts

Ralfe[2] shortly after, though confirming the potassium deficiency in the scorbutic's urine, refuted this potassium food deficiency hypothesis by administering potassium nitrate to scurvy patients without beneficial results This author's study is spoiled for our purposes owing to the fact that the food was not measured or analyzed He, however, studied

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*From the wards of the Montreal General Hospital and the Medical Chemical Laboratory, McGill University, Montreal
*Manuscript submitted for publication March 11 1912

1 Garrod, A B Month Jour Med Sc (Lond & Edinb) 1848, viii, 457
2 Ralfe, C H Lancet, London, 1877, i, 868, ii, 81

in the urine the free acidity, urea, uric acid, and the inorganic constituents, chlorin, sulphuric acid, calcium and magnesium phosphates, potassium and sodium phosphates, and potassium and sodium Ralfe found in the urine of scurvy patients that there is an increase of uric acid, a diminution of the total acidity and a reduction of the alkaline phosphates

Buzzard[3] tried to overcome Ralfe's objection by stating that it was the organic salts of potash that possessed the antiscorbutic powers More recently Hutchison[4] has accepted Buzzard's view and found that a sterilized dialysate of orange juice and to a less degree a solution of malate or tartrate or citrate of potassium had a curative effect Litten[5] writes that the results of the potassium analyses of the urine are very contradictory, further, that phosphoric anhydrid is increased and that beyond a doubt the uric acid content is very high at the height of the disease but diminishes rapidly with the convalescence

Wright[6] maintained that the exclusive feeding with certain foods (as oats, barley, fresh and salt meats) which after incineration left an acid ash, were responsible for the production of scurvy and accordingly regarded it as an acid intoxication

Holst,[11] Frolich[7, 8, 9] and Furst[10] disproved Wright's contention by producing scurvy in guinea-pigs with foods (as peas, almonds, and lentils) yielding an alkaline ash The disease picture both macroscopically and microscopically revealed the characteristic changes of the osseous system found in scurvy-rickets of children Mixtures of nine varieties of dried vegetables with an alkaline ash caused scurvy in from twenty-seven to thirty-one days In the fresh state these vegetables possessed antiscorbutic properties This experimental scurvy could be cured by the administration of barley, peas and lentils which had previously been allowed to sprout Further, raw milk lessened the scurvy produced in guinea-pigs by the exclusive feeding with oats, this antiscorbutic quality of the milk was destroyed by heating to 100 C for ten minutes The authors therefore concluded that scurvy is due to an absence in the food of some constituent possibly of the nature of an enzyme

Nowhere in the literature could we find an accurate study of the mineral metabolism in a case of adult or infantile scurvy Hence we believe that our careful study may prove of some use and stimulate future investigation

3 Buzzard, Thos Reynold's System of Medicine (London), Ed 3, 1876, i, 765
4 Hutchison, Robt Lancet, London, 1904, i, 1253
5 Litten, M Nothnagel's Handbuch der Spec Path u Therap, 1901, viii, 3 277
6 Wright, A E Lancet, London, 1908, ii, 725 and 1365
7 Holst and Frolich Biochem Centralblatt, 1907, vi, 857
8 Holst and Frolich Norsk Mag f Lagev, 1910, 5 R viii, 209
9 Frolich Zentralbl f Biochem u Biophysik, 1910, x, 722
10 Furst Zentralbl f Biochem u Biophysik, 1910, x, 3098
11 Holst Zentralbl f Biochem u Biophysik, 1910, x, 3096

III CLINICAL HISTORY

M M, aged 38 Laborer, Austrian Pole, admitted to Dr H A Lafleur's service in the Montreal General Hospital on July 2, 1909

Entrance Complaint—"Sore Knee"

Family History—Negative

Personal History—The patient was born in Austrian Poland, where he had lived until 1907, when he emigrated to Canada He had always enjoyed good health and denied all acute infections as scarlet, typhoid, and rheumatic fevers, syphilis or purpura For some months prior to his illness he had been working as a day laborer in Blue Bonnets, a little village on the outskirts of Montreal He lived in a shanty with twenty-one other men in one sleeping room, under poor hygienic conditions Their food consisted of fresh meat and beans, but very little if any fresh vegetables, very little salt pork or fish were used As far as the patient knew, none of his companions had sore gums or spots on the skin similar to his

Present Illness began one month before admission when he had pain, swelling and limitation of movement of the left knee joint which he assigned at first to an injury received three months before, which, however, had not laid him up at that time Coincident with the swelling of the knee he noticed for the first time spots on the skin of the thighs as well as soreness of the gums There were no hemorrhages from the mucous membranes or other joint symptoms

Physical Examination July 3, 1909, revealed a fairly well-nourished though somewhat anemic man of about stated age Numerous petechiæ were seen around the hair follicles of both extremities, especially on their anterior surface There was a large subcutaneous purplish ecchymosis behind the lower third of the right thigh and knee joint which on palpation was markedly indurated and slightly tender The left knee joint was much swollen, painful on movement and of a purplish red color A skiagram was negative for periosteal or other bone lesions of that locality On the outer side of the right elbow joint was a small subcutaneous ecchymosis In addition there were numerous small superficial ecchymoses, some quite fresh, over the posterior and inner surfaces of the left thigh On the trunk were a few acneiform papules Just below and to the outer side of the left elbow joint was a subcutaneous nodule the size of a large bean The gums, which bled very easily, were of a dull purplish hue and very spongy they protruded slightly over the teeth, between which they showed the usual tongue-like projections There were two or three dark greenish-black patches of necrosis on the buccal service of the gums The breath was distinctly fetid The teeth were carious but not loose The lymphatic glands were normal except for a slight enlargement of both axillary groups

The other viscera were normal

There was a moderate secondary anemia (Hb, 40 per cent, Sahli, R B C, 2,690,000) while the leukocytes were below normal (4,480)

The temperature ranged between 97 8 and 100 F, and the pulse between 80 and 90 per minute He weighed on admission 137½ pounds The urine was yellow in color, acid in reaction with a specific gravity of 1,008, and contained neither albumen, sugar nor pathological sediment

Treatment—On July 4 the patient was placed on a special diet for purposes of study One week later orange juice was added to the diet

The metabolism experiment ceased July 17 when he was found to weigh 132¾ pounds After this he was given a general ward diet with abundant green vegetables, lemons and oranges The improvement in his general condition was rapid The gums became smaller and of a more healthy color The brawny induration of the right thigh cleared up and the knee joint could be easily flexed and extended The purpuric spots became smaller and were represented for the most part by brownish pigmented areas On July 23, after being up and about the ward for two days, he insisted on going home and was, consequently, discharged

IV CHEMICAL METHODS

Owing to the semiliquid consistency of the stools, it was impossible to accurately separate the feces by means of charcoal, carmin, etc For this reason the experiment was divided into four periods The feces of the first day of the fore-period and of the first two days of the main period of the experiment were collected and analyzed separately During the first and second periods, lasting one and five days, respectively, the patient received the following diet, qualitatively similar to that recommended by Folin [12] (This diet more than fulfils the requirements of the average man of 70 kilos as far as protein and calories are concerned)

	gm or c c
Whole milk	625
Cream (18 to 22 per cent)	375
Eggs (white and yolk)	560
Horlick's Malted Milk	250
Sugar	25
Sodium chlorid	7
Water to	2,500

The mixture was freshly prepared and 2,000 c c administered each day The balance was accurately measured and preserved under 20 c c toluol in bottles with well-fitting ground-glass stoppers These were kept constantly in a refrigerator During the third and fourth periods, lasting two and five days, respectively, the same diet was administered, except that 250 c c of the water was replaced by 250 c c of orange juice A sample of each day's food was analyzed separately

The urine was collected in the ordinary hospital urinal and transferred quantitatively by means of a known quantity of distilled water into a 2 5-liter glass-stoppered bottle and preserved in the refrigerator under toluol At the end of two years the urine was acid and free from bacterial growth On analysis the urine was found to contain in addition to a rather bulky sediment of urates, a relatively heavy one of uric acid In order to obtain a clear solution, we proceeded as follows The bottle was thoroughly shaken and about 500 c c of the urine quickly transferred into a dry round-bottomed flask, the neck of which was drawn out into a tube about 70 cm long and 12 to 13 mm in diameter This tube was surrounded by a glass condensing jacket and cooled with running water The urine could now be heated to boiling without loss of water, which was necessary at times in order to obtain a clear solution, and even then a few crystals of uric acid would remain undissolved The urine in the flask was afterward rapidly cooled to 15 C and transferred to a dry Jena Erlenmeyer flask and the required volume pipetted

The total nitrogen, the ammonia and the total acidity were determined in the freshly collected and unheated urine at the outset of the experiment

12 Folin, Otto Am Jour Physiol, 1905, xiii, 45

The mineral ingredients were analyzed subsequently at our leisure We would here advise that for the preservation of the urine for potassium and sodium analyses, bottles made of Jena or other resistant glass be used

The stools for each period were transferred quantitatively by means of distilled water into a carefully tared desiccator and dried to constant weight in vacuo at 45 to 55 C The desiccator was placed in a water-bath and connected by means of a curved glass tube with a 2-liter distilling flask, the stem of which entered a suction flask containing a little $N/10$ H_2SO_4 solution and a drop of alizarin red The diminished pressure was obtained by means of an ordinary water suction apparatus and the condensation by means of running water

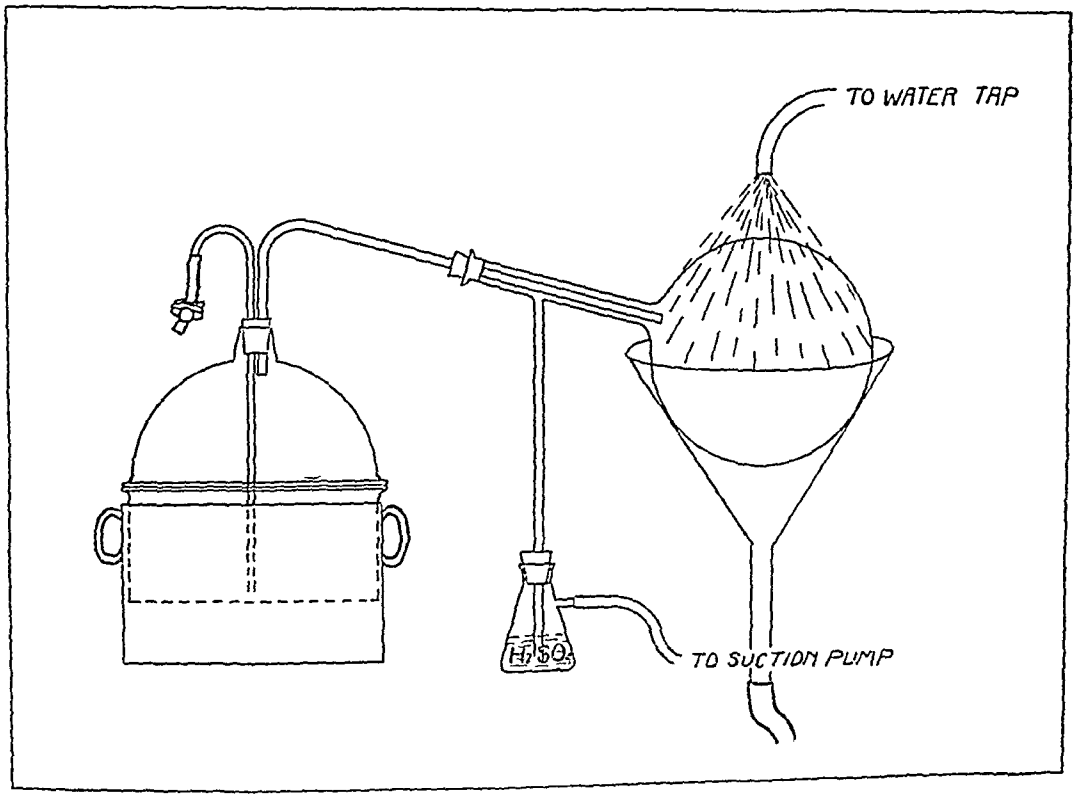

Diagram of desiccator described in text

In this way the feces were dried to constant weight in twelve to thirty-six hours, depending on the quantity On the average, 5 7 per cent of the total nitrogen present in the feces was found in the clear distillate Frothing of the feces was prevented by aeration through the small tube and a few drops of petroleum The total quantity of the dried feces was obtained by subtracting the weight of the empty desiccator from the desiccator and the dried feces The bulk of the feces was removed with a spatula, ground in a mortar and preserved in bottles hermetically sealed with paraffin until analyzed It was not necessary to pulverize the feces as concordant duplicate analyses were obtained with samples containing particles the size of a pea For example, the following results for nitrogen and calcium were obtained

	Amount, gm	Nitrogen	Calcium
Feces I*	1	0 0273	0 0790
	1	0 0269	0 0787
Feces II	1	0 0622	0 0441
	1	0 0626	0 0445
Feces III	1	0 0509	0 0564
	1	0 0509	0 0573
Feces IV	1	0 0427	0 0667
	1	0 0425	0 0665

*The analyses were carried out in duplicate

The homogeneous nature of the liquid food mixture employed was determined by repeated analyses of definite volumes

Analytical Methods.—All analyses were carried out in duplicate and rejected unless the variation between the two analyses was well within the experimental error. The average of the duplicate analyses was selected as the basis for calculation. The maximum variation for each series is given in its proper place. It was computed by selecting the greatest variation between the duplicates of a series and this error calculated for 100 c.c. of urine or food or 100 grams of feces.

1. Urine.—The *nitrogen* was determined according to Kjeldahl, 10 c.c. being used in duplicate. Sodium alizarinsulfonate was used as indicator. The maximum variation for 100 c.c. urine was 0.004 nitrogen.

The *ammonia* was determined according to Folin,[13] 25 c.c. being used and the air passed through the cylinder over night. The indicator used was sodium alizarinsulfonate. The maximum variation between the duplicates for 100 c.c. of urine was 0.003 NH_3.

The *total acidity* was estimated according to Folin[14]. The number of cubic centimeters of N/10 Na(OH) required to neutralize the total quantity of the urine was calculated. The exact end-point in this titration could only be accurately determined after a good deal of experience, the yellow color of the urine obscuring the indicator, phenolphthalein. The maximum variation was 0.8 c.c. N/10 Na(OH) for 100 c.c. urine.

The *total sulphur* was determined according to Benedict[15] with 10 c.c. of urine. This method was found to be more accurate and rapid than the sodium peroxid method used by Folin[16]. The following consecutive analyses are illustrative:

	$BaSO_4$		$BaSO_4$		$BaSO_4$
July 4	0.1000	July 6	0.0944	July 8	0.1031
	0.1000		0.0946		0.1030
July 5	0.0924	July 7	0.0921		
	0.0930		0.0923		

13. Folin, Otto: Z. f. Physiol. Chemie, 1902, xxxvii, 161; P. Schaffer, Amer. J. Phys., 1903, 8, 330.
14. Folin, Otto: Am. Jour. Physiol., 1903, ix, 265.
15. Benedict, S. R.: Jour. Biol. Chem., 1909, vi, 363.
16. Folin, Otto: Jour. Biol. Chem., 1906, i, 131.

The maximum error in duplicate determination was less than 0 001 grams sulphur for 100 c c urine We did not therefore find it necessary to use the modification suggested by Denis [17]

Chlorin was estimated according to Clarke's[18] modification of Dehn's method, 10 c c of urine being used in duplicate The maximum error was 0 004 gm Cl in 100 c c. of urine

Total Phosphorus —The urine was first ashed according to Neumann in Kjeldahl flasks of Jena glass Five c c of concentrated H_2SO_4 was added to 100 c c urine and complete destruction of the organic matter obtained by the gradual addition of concentrated nitric acid The ash and sulphuric acid were transferred to a measuring flask and diluted to 250 c c This solution served for the determination of the total phosphorus as well as the potassium and sodium Twenty-five cubic centimeters of this solution, corresponding to 10 c c of urine, were analyzed according to the volumetric method of Neumann[19] for phosphorus In order to obtain a coarsely granular precipitate of the ammonio-phosphomolybdate which might be easily washed free of acid and filtered, we proceeded as follows

To 25 c c of the Neumann ash solution in a Jena Erlenmeyer flask of 400 c c capacity, 125 c c of water, 50 c c of 50 per cent ammonium nitrate solution, 3 c c of concentrated sulphuric acid and 1 c c of concentrated nitric acid were added The mixture was then heated until bubbles began to appear and then precipitated with 40 c c of 10 per cent ammonium molybdate solution The flask was then shaken until precipitation was complete (about one minute) and allowed to stand for ten minutes, after which it was decanted through Gooch crucibles in the manner suggested by Bayliss and Plimmer [20]

As a rule after four washings the precipitate was free from acid and could then be decomposed and titrated in the usual manner In this way the total phosphorus of the urine, feces and food could be rapidly and accurately determined As many as three duplicate determinations were carried out on the ash solution in ten hours The following five consecutive duplicate analyses illustrate the accuracy of this method

	P_2O_5		P_2O_5		P_2O_5
July 12	0 0398	July 14	0 0408	July 16	0 0398
	0 0400		0 0408		0 0395
July 13	0 0406	July 15	0 0414		
	0 0407		0 0420		

The maximum error was 0 005 gm phosphorus for 100 c c urine

Sodium and Potassium —These were determined on the Neumann ash solution mentioned above Twenty-five c c of the solution (equivalent to 10 c c urine) was evaporated in a platinum dish and the sulphuric acid

17 Denis, W Jour Biol Chem , 1910, viii, 401
18 Clark, S Hawk's Practical Physiol Chem Ed 3, 1910, p 388
19 Neumann, A Ztschr f Physiol Chem , 1902-3, xxxvii, 129, 1904-5, xliii, 35
20 Bayliss and Plimmer Jour Physiol , 1905-6, xxxiii, 441

completely volatilized The residue was dissolved in a little distilled water, transferred to a Jena Erlenmeyer flask to which was added 5 c c of concentrated HCl and 100 c c of water, this solution was now boiled and the SO_4 ions were precipitated by the gradual addition of barium chlorid through the Folin automatic dropper[21] When cool the barium sulphate was filtered off through an ashless filter into a platinum dish the precipitate was now washed thoroughly and the washings and filtrate evaporated to dryness on the water-bath to remove the bulk of the hydrochloric acid The residue was again dissolved in water, transferred to a Jena Erlenmeyer flask, to which 100 c c of water was added, then heated to boiling and precipitated by the gradual addition (drop method) of 20 c c of a half saturated solution of chemically pure barium hydrate obtained by double recrystallization When cold it was filtered and washed thoroughly The filtrate and washings were treated with an ammoniacal solution of ammonium carbonate (made by passing dry CO_2 into a 15 per cent solution of NH_4) until no further precipitation occurred After two hours the precipitate was then filtered off, washed thoroughly and the filtrate and washings evaporated carefully to dryness on the water-bath, avoiding a too rapid decomposition of the ammonium carbonate The residue was again treated with about 10 c c of the ammoniacal ammonium carbonate solution for two hours, any resulting precipitate filtered and the filtrate and washings again evaporated to dryness The residue was taken up in water, transferred to a weighed platinum crucible, evaporated to dryness on the water-bath and the ammonium salts volatilized When the weight of the crucible was constant, the weight of the chlorids of the potassium and sodium was noted, they were then dissolved in a little water and filtered, as a small amount of insoluble residue was always present The filter and residue were washed thoroughly, dried and incinerated and the weight of the ash deducted from the weight of the sum of the chlorids of potassium and sodium

The potassium was determined as potassium platinic chlorid (K_2PtCl_6) In this way acceptable results were obtained with a standard solution containing potassium and sodium chlorid, acid potassium phosphate, sulphuric acid, calcium carbonate and magnesium sulphate in about the proportions in which they occur in the ash solution to be analyzed

	NaCl	KCl
Solution I contained	0 1011	0 0692
found	0 1016	0 0694
found	0 1003	0 0691
found	0 1016	0 0694
Solution II contained	0 0809	0 0553
found	0 0806	0 0552
found	0 0814	0 0550
found	0 0811	0 0553

21 Folin, Otto Jour Biol Chem, 1906, i, 131

The maximum error for sodium was 0 005 and for potassium 0 009 for 100 c c of urine

Calcium and Magnesium—Fifty c c of urine were analyzed directly for calcium and magnesium according to the method of McCrudden [22] We can fully corroborate the author's claim for the accuracy of his method For seven consecutive duplicate analyses we obtained the following

	MgO	CaO
July 4	0 0107	0 0117
	0 0107	0 0117
July 5	0 0074	0 0120
	0 0073	0 0122
July 6	0 0069	0 0129
	0 0072	0 0129
July 7	0 0069	0 0123
	0 0072	0 0125
July 8	0 0087	0 0142
	0 0088	0 0146
July 9	0 0080	0 0146
	0 0080	0 0146
July 10	0 0078	0 0141
	0 0078	0 0141

The Aron[23] method for determining calcium as $CaSO_4$ proved entirely unsatisfactory in our hands

2 Food For the *total nitrogen* 5 c c was taken in duplicate and determined by Kjeldahl's method

For the *total sulphur*, 5 c c was also taken and determined by Benedict's method with the following results

	$BaSO_4$, gm		$BaSO_4$, gm		$BaSO_4$, gm
July 8	0 0228	July 10	0 0216	July 12	0 0206
	0 0228		0 0220		0 0213
July 9	0 0226	July 11	0 0224		
	0 0222		0 0228		

The maximum error was 0 003 gm sulphur for 100 c c of food

The *total chlorin* was determined in duplicate, using 5 c c of food The sodium peroxid method was used and chlorin weighed as silver chlorid (AgCl) The maximum error was 0 006 gm of chlorin for 100 c c of food

The *phosphorus* was determined in 100 c c of the food by ashing according to Neumann and the ash and sulphuric acid diluted to 250 c c Of this solution 25 c c in duplicate were analyzed in the manner above described The maximum error was 0 003 gm of phosphorus for 100 c c of food

The *sodium and potassium* were determined in the same manner as in the urine using 25 c c of the ash solution or 10 c c of food in duplicate The following five consecutive results were obtained

22 McCrudden, F Jour Biol Chem, 1910 vii, 83
23 Aron, H Biochem Ztschr, 1907, iv, 268

	NaCl, gm	KCl, gm
July 4	0 0530	0 0351
	0 0529	0 0352
July 5	0 0499	0 0359
	0 0497	0 0367
July 6	0 0529	0 0424
	0 0530	0 0429
July 7	0 0512	0 0368
	0 0519	0 0361
July 8	0 0450	0 0360
	0 0456	0 0369

The maximum error was 0 0027 gm for sodium and 0 0057 gm for potassium for 100 c c of food

The *calcium and magnesium* in the food were determined as follows Twenty-five c c of the food was allowed to dry on a platinum dish on the water-bath for from twelve to fifteen hours, it was then gradually charred and extracted with dilute hydrochloric acid The residue was now gradually incinerated until a grayish white ash with a few black particles remained, to this the hydrochloric acid extract was added and the whole evaporated and allowed to dry in an oven at 110 C for two hours to render any silicic acid insoluble The ash was then dissolved in about 100 c c of water containing 3 c c concentrated hydrochloric acid, filtered and analyzed for calcium and magnesium by McCrudden's method The maximum error was 0 0017 gm calcium and 0 0007 gm magnesium for 100 c c of food

3 *Feces Nitrogen* was determined in 10 c c of the distillate obtained from the feces while drying in vacuo, as well as in 1 gm of the dry feces, the maximum error for 100 gm of the dried feces being 0 040 gm of nitrogen

Sulphur —From 0 5 to 1 5 gm of the dried feces was treated with 20 c c of fuming nitric acid in a Kjeldahl flask and a small amount of heat applied until the solid matter had disappeared and the brown fumes had considerably decreased The solution was then transferred to a 100 c c porcelain evaporating dish, to which 20 c c of Benedict's solution and 2 gm of C P sodium chlorid were added, the whole evaporated to as complete dryness as possible, then very gradually heated to redness, and when cold covered with a watch glass and dissolved in dilute HCl, filtered and precipitated in the usual manner The four specimens examined by this method gave the following sulphur value for 1 gm of dried feces

I	0 0043	III	0 0083
	0 0044		0 0084
II	0 0061	IV	0 0040
	0 0061		0 0041

Maximum error for 100 gm dried feces = 0 0100 sulphur

The sodium chloiid was added to prevent loss by deflagration which regularly occurred in the trying out of Wolff and Osterberg's modification of Benedict's method [24]

Chloiin—From 1 to 1 5 gm of the dried feces was weighed into a platinum dish, 25 c c of a 10 per cent solution of C. P sodium carbonate added and the whole evaporated to dryness on the water bath, then gradually incinerated, avoiding red heat The cold ash was extracted with dilute nitric acid under a watch glass, the residue heated until white, the acid extract added and the whole evaporated to dryness, then heated to 110 for two hours, taken up in dilute nitric acid, filtered and precipitated with silver nitrate solution. When cold and the precipitate had settled, the silver chlorid was filtered through a tared Gooch crucible, dried at 120 C and weighed The four samples analyzed gave the following chlorin values for 1 gm of dried feces

I	0 0099	III	0 0150
	0 0101		0 0143
II	0 0215	IV	0 0062
	0 0212		0 0060

The maximum error was 0 070 chlorin for 100 gm of the dried feces

Phosphorus was determined according to Neumann, as in the case of the urine and food The maximum error was 0 040 gm of phosphorus for 100 gm of the dried feces

Sodium and Potassium—The same method was used as for urine and food The maximum erior was 0 040 per 100 gm dried feces, for sodium, and 0 050 per 100 gm dried feces for potassium

Calcium and Magnesium—Dry ashing was resorted to The subsequent steps were identical with those previously described under the calcium and magnesium deteimination in the food The maximum error for calcium was 0 028, and for magnesium, 0 024 for 100 gm of dried feces

V PROTOCOLS

(See Protocols 1 and 2)

VI DISCUSSION

Having selected a diet qualitatively similar to that administered by Folin[12] in his metabolism experiments on the normal man, we have the opportunity of comparing our results, to some extent, with his

Total Nitrogen The nitrogen ingested was fairly constant throughout the experiment, the average daily intake ranging between 19 13 and 19 51 gm The average daily excretion during the fore-period was 15 26 gm in the urine and 4 07 gm in the feces, i e, about 21 per cent of the total nitrogen excreted appeared in the feces There was, therefore, a positive balance or nitrogen retention of 0 85 gm N for the

24 Wolff, C, and Osterberg, Emil Biochem Ztsphr, 1910, xxix, 429

Date, July, 1909	Urine 10— Volume of Urine	Nitrogen Output				Ammonia Nitrogen of Urine	Ammonia Nitrogen in per cent of Total Nitrogen	Total Acidity of Urine in c c of N/ Sodium Hydrate	Chlorine Output				Sulphuric Acid Output				Remarks
		Intake	Urine	Feces	Balance				Intake	Urine	Feces	Balance	Intake	Urine	Feces	Balance	
4	23 865	19 42	13 82	1 17	+4 43	0 89	6 4	*	1 23	1 19	0 17	—0 13	6 95	3 33	0 40	3 22	Milk,
5	26 920	19 82	13 29	4 07	+2 46	0 66	4 9	477	1 28	1 17	0 36	—0 25	6 52	5 70	1 25	—0 43	Cream
6	25 960	21 62	13 79	4 07	+3 76	0 83	6 0	521	1 30	1 24	0 36	—0 30	6 83	5 78	1 25	—0 20	and
7	26 1030	18 18	15 73	4 07	—1 62	0 89	5 7	656	1 25	1 30	0 36	—0 41	6 60	6 87	1 25	—1 52	Egg
8	28 910	19 36	15 59	4 07	—0 30	0 89	5 7	705	1 32	1 29	0 36	—0 33	5 94	4 92	1 25	—0 23	Diet
9	25 1070	18 53	17 91	4 07	—3 45	0 93	5 2	710	1 29	1 47	0 36	—0 51	6 11	6 37	1 25	—1 18	2,000 c c
Daily Average	26 978	19 51	15 26	4 07	+0 18	0 84	5 5	613 8	1 29	1 29	0 36	—0 36	6 47	5 93	1 25	—0 71	period
Balance for period					+0 85							—1 83				—3 56	
10	25 1096	18 96	17 92	1 02	+0 02	0 93	5 2	743	1 26	1 42	0 16	—0 32	6 64	6 56	0 28	—0 20	Milk,
11	24 1030	19 61	15 26	1 02	+3 33	0 91	6 0	529	1 32	1 30	0 16	—0 14	6 31	5 94	0 28	+0 09	Cream and
Daily Average	245 1063	19 29	16 59	1 02	+1 68	0 92	5 6	636	1 29	1 36	0 16	—0 23	6 48	6 25	0 28	—0 06	Egg
Balance for period					+3 35							—0 46				—0 11	Diet
12	26 1168	19 22	17 86	1 45	—0 09	0 85	4 7	696	1 22	1 57	0 14	—0 49	6 16	5 85	0 20	+0 11	
13	27 930	19 75	14 35	1 45	+3 95	0 87	6 0	450	1 43	1 25	0 14	+0 04	6 94	5 11	0 20	+1 63	1,800 c c
14	26 1190	19 27	18 45	1 45	—0 63	1 11	6 0	696	1 36	1 66	0 14	—0 44	7 23	5 95	0 20	+1 08	+200
15	30 1080	18 98	17 37	1 45	+0 16	1 22	7 0	526	1 41	1 55	0 14	—0 28	6 87	6 77	0 20	—0 10	c c
16	30 990	18 45	16 85	1 45	+0 15	0 92	5 5	569	1 30	1 45	0 14	—0 29	6 30	5 79	0 20	+0 31	Orange
Daily Average	28 1072	19 13	16 98	1 45	+0 71	0 99	5 8	587	1 35	1 50	0 14	—0 29	6 70	5 89	0 20	0 61	Juice
Balance for period					+3 54							—1 46				3 03	period

PROTOCOL 2.—SHOWING INTAKE, OUTPUT AND BALANCE OF PHOSPHORUS, SODIUM, POTASSIUM, CALCIUM AND MAGNESIUM

Date 1909	Total Phosphorus				Sodium				Potassium				Calcium				Magnesium				Remarks
	Intake	Output		Balance	Intake	Output		Balance	Intake	Output		Balance	Intake	Output		Balance	Intake	Output		Balance	
		Urine	Feces			Urine	Feces			Urine	Feces			Urine	Feces			Urine	Feces		
4	2 53	1 49	1 09	—0 05	4 39	2 56	0 24	+1 59	3 88	1 78	1 08	+1 02	1 84	0 14	2 23	—0 53	0 32	0 11	0 17	+0 04	Milk,
5	2 61	1 14	1 15	+0 32	4 13	4 03	0 80	—0 70	4 01	1 95	1 53	+0 53	1 93	0 16	1 85	—0 08	0 35	0 08	0 25	+0 02	Cream
6	3 23	1 45	1 15	+0 63	4 42	4 16	0 80	—0 54	4 74	2 06	1 53	+1 15	2 68	0 18	1 85	+0 65	0 36	0 08	0 25	+0 03	and
7	2 61	1 75	1 15	—0 29	4 30	4 70	0 80	—1 20	4 05	2 39	1 53	+0 13	1 92	0 18	1 85	—0 11	0 29	0 09	0 25	—0 05	Egg
8	2 75	1 79	1 15	—0 19	3 76	3 54	0 80	—0 58	4 03	2 31	1 53	+0 19	1 94	0 19	1 85	—0 10	0 31	0 10	0 25	—0 04	Diet
9	2 60	1 95	1 15	—0 50	4 18	4 23	0 80	—0 85	4 00	3 00	1 53	—0 53	1 89	0 22	1 85	—0 18	0 33	0 10	0 25	—0 02	2,000
Daily Aver	2 76	1 62	1 15	—0 006	4 16	4 13	0 80	—0 77	4 17	2 34	1 53	+0 29	2 07	0 19	1 85	+0 036	0 33	0 09	0 25	—0 012	c c p d
Bal f period				—0 03				—3 87				+1 47				+0 18				—0 06	
10	2 59	1 90	0 47	+0 22	4 22	3 93	0 20	+0 09	4 52	3 75	0 40	+0 37	1 85	0 22	0 78	+0 85	0 32	0 10	0 10	+0 12	Milk,
11	2 66	1 53	0 47	+0 66	4 18	3 63	0 20	+0 35	4 75	3 31	0 40	+1 04	1 97	0 22	0 78	+0 97	0 37	0 12	0 10	+0 15	Cream
Daily Aver	2 63	1 72	0 47	+0 44	4 20	3 78	0 20	+0 22	4 64	3 53	0 40	+0 71	1 91	0 22	0 78	+0 91	0 345	0 11	0 10	+0 135	and
Bal f period				+0 88				+0 44				+1 41				+1 82				+0 27	Egg
12	2 62	2 03	0 76	—0 17	3 92	3 81	0 080	+0 03	4 45	3 90	0 56	—0 01	1 99	0 24	1 55	+0 20	0 35	0 15	0 21	—0 01	Diet
13	2 65	1 65	0 76	+0 24	4 38	3 43	0 080	+0 87	4 56	3 32	0 56	+0 68	1 92	0 17	1 55	+0 20	0 37	0 11	0 21	+0 05	1,800
14	2 66	2 12	0 76	—0 22	4 67	4 10	0 080	+0 49	4 62	3 49	0 56	+0 57	1 82	0 24	1 55	+0 03	0 36	0 19	0 21	—0 04	c c +
15	2 62	1 97	0 76	—0 11	4 60	4 45	0 080	+0 07	4 97	3 71	0 56	+0 70	2 00	0 20	1 55	+0 25	0 41	0 16	0 21	+0 04	200 c c
16	2 50	1 71	0 76	+0 03	3 99	3 64	0 080	+0 27	4 49	3 51	0 56	+0 39	1 95	0 18	1 55	+0 22	0 38	0 15	0 21	+0 02	Orange
Daily Aver	2 61	1 90	0 76	—0 046	4 31	3 89	0 080	+0 35	4 62	3 59	0 56	+0 47	1 94	0 21	1 55	+0 18	0 37	0 15	0 21	+0 012	Juice
Bal f period				—0 23				+1 73				+2 33				+0 90				+0 06	period

whole period During the second part of the fruit juice period 16 98 gm were excreted per diem in the urine, while only 1 45 gm (or 7 8 per cent of the total N) was present in the feces A more marked positive balance (3 54 gm for the period) was present after the administration of orange juice Laurenti[25] has recently found, following the administration of various fruit juices, an increase in the output of both the total nitrogen and the uric acid in the urine, though no mention is made of the analyses of the feces or of the food in the abstract of his paper In our case the urine nitrogen was increased during the fruit juice period but this was counterbalanced by the diminution of the nitrogen in the stools

Ammonia Nitrogen The ammonia nitrogen was slightly increased, both relatively and absolutely, but no marked difference between the periods is noticeable The average daily ammonia-nitrogen excretion for Period II was 0 84, for Period IV, 0 99, as compared with Folin's average of 0 70 The ammonia coefficient was 5 5 for Period II and 5 8 for Period IV Folin's average was 4 3 From these data one can unquestionably exclude an acidosis, as is claimed by Wright

Total Acidity The total acidity of the urine was somewhat lower for the fruit juice period, 587, as compared with 613 8 for the preliminary period Folin's average was 617, and his minimum acidity, 554

Sulphur Metabolism This was rather unusual With the exception of one day, more sulphur was eliminated than ingested At first we attributed this result to an analytical error, but further control determinations substantiated this finding During Periods II and IV, respectively, an average daily loss of 0 36 and 0 29 occurred, leading to a minus balance of 1 83 and 1 46 gm of sulphur for Periods II and IV, respectively, whereas the nitrogen balance was positive for both periods The daily sulphur eliminated with the feces during Period II was 0 36 gm or 21 9 per cent of the total Of the sulphur eliminated during the fruit juice period only 0 14 gm were passed per rectum This amounts to 8 5 per cent of the total sulphur elimination For want of material we were, unfortunately, unable to examine the sulphur partition

Chlorin The chlorin ingestion was fairly constant, 6 47 gm during Period II and 6 70 gm during Period IV being the average daily intakes The urinary chlorin excretion was practically similar for both periods, being 5 9 gm Folin's daily average was 6 1 Here, again, we have the better utilization during the fruit juice period for only 0 20 gm were lost through the feces, i e, 3 1 per cent of the chlorin eliminated, whereas during the preliminary period 1 25 gm or 17 4 per cent of the total chlorin excreted was present in the feces The average daily loss for Period II was 0 71 gm, compared with an average daily gain of 0 61 gm for Period IV

25 Laurenti, T Policlinico (Rome), 1912, xix, 525, Abstr in Jour Am Med Assn, 1912, lviii, 452

Total Phosphorus The average daily intake varied between 2 76 and 2 61 gm The daily urinary phosphorus averaged 1 62 and 1 90 gm for the respective periods, while 1 15 gm was the average daily amount passed in the feces during Period II as compared with 0 76 gm during Period IV The balance was slightly negative throughout, 0 006 and 0 046 being the average daily losses during Periods II and IV, respectively

Sodium The average daily intake varied between 4 16 and 4 31 gm for Periods II and IV, respectively During the former 16 2 per cent, and during the latter only 1 7 per cent was lost through the feces During the Period II the balance was negative (— 3 87), equivalent to an average daily loss of 0 77 gm During Period IV the balance was positive (+ 1 73), equivalent to an average daily gain of 0 35 gm

The sodium behaved very much like the chlorin, as one would expect

Potassium The intake varied between the daily average of 4 17 for the preliminary period and 4 62 for the fruit juice period A much larger percentage of the excretion occurred through the feces than was the case with sodium During Period II, 1 53 gm (or 39 5 per cent of the total excretion) was the average daily amount present in the feces During Period IV, 13 5 per cent was lost in the feces The balance was positive throughout, + 0 29 and + 0 47 gm being the average gains for Periods II and IV, respectively

Calcium Here the excretion took place largely through the intestine, as one would expect, 0 19 and 1 85 gm was the average daily excretion in the urine and feces, respectively, during Period II, contrasted with 0 21 and 1 55 for Period IV The balance was positive throughout but greater during Period IV (0 90), as compared with Period II (0 18)

Magnesium Here again 0 25 gm was excreted in the feces and 0 09 in the urine during Period II as compared with 0 21 and 0 15 during Period IV The balance was negative during the former (— 0 06) and positive during the latter (+ 0 06) periods

VII CONCLUSIONS

As this is the first accurate study of the metabolism of scurvy, it would be hazardous to venture any conclusion from the above figures

In our experiment the loss of the various food constituents through the feces was less when the fruit juice was added to the diet The total sulphur metabolism was abnormal throughout Chlorin and sodium were retained during the fruit juice period, but excreted in excess of the intake during the preliminary period More potassium, calcium and magnesium were retained during the fruit juice period

If an opportunity presents, we hope to acquire additional data and possibly substantiate the above figures Finally, we take pleasure in thanking Prof H A Lafleur for his kind permission to study the case in his ward, and Prof R F Ruttan for the use of the laboratory, and for various pertinent suggestions

TUBERCULOSIS OF THE SPLEEN[1]

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Tuberculosis of the spleen may be primary or secondary By primary it is not meant that the spleen is the portal of entry of the organism, or even the first tissue of the body in which the disease manifests itself, but that the diseased process may localize itself in the spleen and not only bring about various lesions but act as a focus for dissemination of the bacilli, while the original focus may be healed entirely It is this type of the disease which we may speak of tentatively as primary tuberculosis of the spleen It occurs most frequently in adults may manifest itself as several distinct clinical types and is characterized by rather typical symptoms and signs In many instances the individual may be cured by splenectomy

A brief review of the occurrence and pathological anatomy of secondary tuberculosis of the spleen will make certain phases of our subject clearer

SECONDARY TUBERCULOSIS OF THE SPLEEN

A Occurrence—Secondary tuberculosis of the spleen is by no means uncommon Cruveilhier considered that next to the lymphatic glands the spleen was the abdominal organ most often affected with tuberculosis As a means of emphasizing this he aptly compared the spleen to the lungs the first being to the abdomen what the second are to the chest Reinhold, quoting from the compiled statistics of the University of Kiel, from 1873 to 1889 as published in the Theses of Simmonds (Kiel 1879), Schwer (Kiel, 1884), Boltz (Kiel, 1890), Plambeck (Kiel, 1885), and Haman (Keil, 1890), says that of 428 cases of tuberculosis in children from 0 to 15 years, the spleen was affected 280 times (66 7 per cent), and of 836 cases of tuberculosis in adults from 16 to 90 years the spleen was affected 160 times (19 1 per cent) Caseous masses are much less frequent, and quoting from the same statistical records, they occurred in 5 7 per cent of tuberculous children (twenty-four out of 421), and in only 1 2 per cent of adults (ten out of 836 cases) Papavonie reported the occurrence of splenic involvement in twenty out of fifty children dead of tuberculosis, or 40 per cent Rillet and Barthez give a lower proportion, finding only 107 cases of splenic involvement out of 312 cases of tuber-

[1]Manuscript submitted for publication March 1, 1912
[2]From the Pathological Laboratory of the Johns Hopkins University

culosis in children Of these it occurred two and one-half times more frequently in boys than in girls

B Pathological Anatomy—The pathology of secondary tuberculosis of the spleen has been reviewed by Bezançon [1] He says the condition of the spleen is extremely variable in the different types of tubercular infection In the granular form in which the tuberculosis occurs as an acute general infection comparable to typhoid fever for example, the spleen is invaded by the bacilli of Koch, and is profoundly altered in its structure, as are all the other organs of the body On the contrary, when the tuberculosis is localized in either the viscera, glands or skin the spleen either does not contain the bacilli or contains them in small numbers The lesions then are much slighter and are due to toxins liberated by the tubercle bacilli or other organisms, secondary invaders, for instance, which are associated with the tuberculosis

1 The Spleen in Acute Generalized Tuberculosis

The fundamental characteristics of the spleen in this type of the disease are hypertrophy and the presence of miliary granules in its parenchyma In the cases observed by Bezançon, the organ attained the weight of 400 to 1,000 gm If the disease has been very acute the spleen may be exactly like a typhoid spleen, it is either firm and resistant with a distended capsule, or it is soft and diffluent The surface is red On section numerous tubercles may be seen, or they may be so small that they are invisible to the naked eye When death follows less rapidly, these nodules are larger and give the organ a mottled appearance, caseous yellow areas being interspersed throughout the congested pulp Histologically the picture varies likewise Before the caseous masses are evident the spleen is a picture of great congestion, the sinuses are tremendously distended with blood and in some places true apoplexies occur as in typhoid fever Even phagocytes laden with red blood-cells occur in abundance The malpighian corpuscles may be little changed or they may show in their interior, epithelioid cells and occasional giant cells Some may show caseation Later in the infection most of the malpighian corpuscles seem to have vanished, in reality they have become the seat of tubercles The tubercles develop at the side of the central artery and are in general rare in the pulp Throughout the pulp there is a great increase in leukocytes These often show division Macrophages are rare, and phagocytosis not abundant The congestion is intense, and hemorrhages may occur

When death from acute tuberculosis is slower, the spleen is different The malpighian corpuscles are replaced by large tubercles These are composed of caseous masses nuclear débris and a few epithelioid and

1 Bezançon's report is given in great detail in Bender's article Gas d hôp 1900 lxxii 375, from which the following review was obtained

giant cells These tubercles may show practically no reactive process at their periphery The tissue of the pulp between the tubercles is engorged, and the lymphatic cells of the pulp have entirely disappeared There remains then only the fibro-areolar structure, engorged with blood Tubercle bacilli occur in such spleens in abundance

2 *The Spleen in Localized Tuberculosis*

In pulmonary tuberculosis of adults the spleen is rarely hypertrophied More often it is diminished in volume, atrophied and indurated Tubercular lesions are rare, but may be found in the form of miliary or caseous conglomerate tubercles In some cases of pulmonary tuberculosis there may be an increase in the volume of the spleen without any tubercular or amyloid infiltration This is due to secondary infection In young children the spleen is increased in size, even in the chronic form of tuberculosis (Landouzy and later Queyrac)

PRIMARY TUBERCULOSIS OF THE SPLEEN

The above described types of secondary tuberculosis of the spleen remained for a long time the only recognized conditions Just as it had been considered that the spleen was the abdominal organ of predilection for the localization of secondary tuberculosis, so it was thought the spleen could not be the seat of a primary infection Gradually, however, with the appearance of isolated case reports by Coley, in 1846, Monneret in 1859, and others, a condition began to be recognized in which at autopsy only a severe tuberculosis of the spleen with practically no involvement of the organs and tissues usually affected by the disease, occurred From the publication of case reports, the knowledge slowly graduated with more detailed studies, such as the one of Quenu and Baudet In 1898 these authors collected five cases, including one of their own, of the nature above described They described clearly this new chapter in pathology and emphasized particularly the possibility of curing this condition by extirpation of the spleen This was of particular interest, since it had been generally supposed that tuberculosis of the spleen was practically always secondary, and could therefore never offer a condition for the application of therapy (Litten)

Still another phase was added to this subject by Rendu and Widal in 1899 These authors described a symptom-complex including tuberculosis of the spleen, polycythemia without leukemia, and cyanosis

From this time on the subject was enriched, not only with case reports, but with reviews of the literature and discussions of the symptoms and therapy of the condition The French writers, especially, have been prolific in this field Bayer, the only German author who has written in any detail on this subject, succeeded in 1900 in collecting nine oper-

ative cases, with seven recoveries, including one of his own, and nineteen autopsy cases He emphasized the importance of splenectomy, and also the relative importance of polycythemia and cyanosis

In the American literature there exist only the excellent case reports by Hayden, 1897, and Stewart, 1901, and the doubtful case by Biggs The subject has assumed considerable importance of late years, and numerous cases have been reported by both the French and Germans All of the cases published (except a few inaccessible ones) are included in the accompanying table, which has been made rather elaborate in the hope of presenting them in a more readily accessible manner [2]

It will be seen at a glance over the table that in order to accumulate these fifty-one cases it has been necessary to assume an extremely liberal attitude In many instances the detail has been so meager that a strict judgment of the case has been impossible The vast majority of the cases are definite instances of massive tubercular involvement of the spleen without any marked involvement of other viscera Then there are cases such as Stewart's and Colet and Gallivarden's in which the notes are in sufficient detail to confirm the author's statement that the other viscera which were the seat of tuberculosis at autopsy became involved after the spleen It is these cases particularly that necessitate hesitancy in discarding other similar instances, such as the cases of Olmer, Vigoroux and Colet, etc, in which the clinical details are insufficient Then there are those cases which remain much in doubt, such as the one reported by Biggs and extensively quoted throughout the literature Biggs' report is very brief and obscured by the following sentence "In other parts of the body the tubercles also showed a tendency to grow to an unusual size" There remains another group of cases in which the autopsy record is insufficient, such as those of Aubertin and Rollin, or totally lacking as in the cases in which the patients recovered after operation, etc

Nevertheless, each one of these cases has been included by some writer in his review of the literature, and since the most inclusive report thus far is that of Bayer, who only has twenty-eight cases, several of which such as the one of Carle, are extremely unsatisfactory, it seems the more worth while to gather all the cases together

It should be mentioned that there are cases published under various titles which probably belong to this group Sternberg,[3] for instance, includes several cases of massive tuberculosis of the spleen with only

2 There are several other cases listed in the literature which probably should be included in the table These have been inaccessible They are 1 Carbone Rassegna de Sc Med Modena 1901-2, xvi, 96, 2 Fredga Upsala Lokaref Forh 1901-2 N F vii, 434, 3 Romanoff Russk Viach, St Petersb 1902, i 1477 4 Brunker Rev méd et pharm de l'Afrique du Nord Alger, 1899, ii 97

3 Sternberg Concerning a Peculiar Form of Tuberculosis of the Lymphatic Tissue Running a Course Similar to Pseudoleukemia, Ztschr f Heilk, 1898 xix 20

slight glandular or pulmonary involvement, which perhaps may belong to the type of tuberculosis which is included in this paper It would lead too far and involve an unfruitful labor to analyze these further and for the present purpose the cases in the accompanying table will suffice

ANALYSIS OF TABLE

Age and Sex —The following tabulation represents the age in decades of the forty-five cases in which it is stated

Age Period	No of Cases	Males	Females	Unknown
1 10	5	3	1	1
10 20	3	1	2	0
20-30	12	3	8	1
30 40	10	5	5	0
40 50	6	4	2	0
50 60	2	3	0	0
60 70	5	2	2	0
70 80	1	1	0	0

It is evident that while the disease may occur at any age, the limits in the above fifty-one cases being 1 year (Coley) and 80 years (Romanow) by far the greater number occur in adults between the ages of 20 and 40 (50 per cent) The cases are evenly distributed between the two sexes It is stated in forty-four instances, and of these there are twenty-two males and twenty-two females

Race —This is only stated positively in three instances Two of these were colored individuals and the other white

Symptoms of Onset —These were given in thirty-nine of the fifty-one cases Pain in the splenic region occurred seven times (18 per cent) Tumor alone eight times (20 5 per cent), and pain and tumor thirteen or 33 3 per cent If these be added there will be twenty-eight cases, or 71 79 per cent in which either pain or tumor in the splenic region, or both, were the symptoms of which the patient complained In several instances the pain was more definite as in Case 47 (Franke) in which there was pain on sitting or in 51 (Strehl), in which there was pain on eating, or 50 (Fischer), in which the pains radiated down the left side The pain in these cases is explained by the pressure of the enlarged spleen on the surrounding structures, especially when these are brought in closer contact, as, for instance, when the stomach is dilated with food or when the abdominal contents are brought closer in contact on sitting In the same way the *gastric disturbances* which occurred in six cases or the *respiratory disturbances* in two cases are to be explained *Loss of weight, weakness,* and *lassitude* were striking features of the early part of the disease, in ten, two, one, and one instances respectively

In striking contrast to the above group is another in which the symptoms of onset were much more severe and characteristic of an acute infectious process This is illustrated in Case 4 (Scharold) in which

there was fever, sweating, cough and collapse, and in Case 12 (Stewart) in which there was fever, backache, and splenic enlargement This group is much smaller than the first group

Between these two types there are a few cases which can hardly be classified with either, for their symptoms were neither as chronic as those of the first group nor as acute as those of the second Our own case and the cases of Brute and Reinhold are of this type The symptoms of onset were loss of weight or appetite, lassitude, anemia, fever, etc In Case 4 (Courmont, Tixier, and Bonnet) the enlargement of the cervical glands was first noticed, and in this way it is an exception to the other cases It will be seen, however, that in most instances there was some glandular enlargement, and for this reason the case is no marked exception

Course.—The duration of the disease varied within wide limits Of the thirty-eight instances in which it is stated, the shortest illness was in the case of Scharold, in which death occurred in seventeen days Then follow the cases of Stewart and Bloch, which also had a short course Bayer's case was of short duration, but since splenectomy was followed by recovery, it is impossible to say what the further course of the disease might have been Just so in Hagan's case, for it was impossible to remove the spleen at operation, and it is possible that the partial removal may have disseminated the infection and influenced its subsequent course

In the next group of cases, including those of Brute, Moutard, Martin and Lefas, Reinhold, Palumbo, van de Vilde Coosemans, Olmer and our own the duration varied from six to nine months As a rule the symptoms of a general infection were much less evident in these cases In a large majority however, the course was very chronic, characterized by enlargement of the spleen and pain in the left hypochondrium Tumor of the spleen may have been present for a long time — fourteen years in Cominotti's case and eight years in the cases of Rendu and Widal and Auche

CLINICAL EVIDENCE OF TUBERCULAR INVOLVEMENT OF OTHER ORGANS OR TISSUES

Lungs.—In forty of the fifty-one instances a note on the lung was found Of these forty the clinical findings were negative in twenty instances (50 per cent) A quiescent lesion was found in three cases (7 5 per cent) and signs of pulmonary involvement developed while under observation in three cases (7 5 per cent) There was a chronic pleurisy in two cases (5 per cent), râles in two cases (5 per cent) cough in one case (2 5 per cent) bronchitis in one case (2 5 per cent) and extensive pulmonary involvement in five cases (12 5 per cent) three of these cases developed signs of pulmonary involvement after the splenic involvement had been demonstrated In the other two cases the authors considered the splenic involvement as antedating the pulmonary

Lymph-Nodes.—The lymph-nodes are mentioned in thirty-five cases. They were normal in twenty-nine instances (82.8 per cent.). In one instance a gland in the supraclavicular fossa developed while the patient was under observation, and in five instances (14 per cent.) there was definite enlargement of the lymph-nodes when the patient came under observation.

Elsewhere.—In thirty-seven cases the reports are complete enough to determine whether there was any definite tubercular process elsewhere. In eighteen of these (48.6 per cent.) there was no clinical evidence of other involvement. In seven (18.9 per cent.) the liver was enlarged, in five (13.5 per cent.) there was ascites. (Two of these cases were unassociated with liver enlargement.) In one (2.7 per cent.) there was a chronic vulvar ulcer considered as a probable source of the infection, in one, caries of the spine, in two meningitis. (Stewart's case developed meningeal symptoms as a terminal event, while in the case of Courmont, Tixier and Bonnet, this is not definitely stated) and in one there were intestinal ulcers. (In this case, reported by Vigoroux and Colet, the authors consider the pulmonary and intestinal lesions to be acute and secondary to a chronic involvement of the spleen.)

Of the fifty-one cases no mention is made concerning pulmonary glandular or other involvement in nine cases (17 per cent.) and they are reported as negative in ten cases (19 per cent.).

Fever.—In nineteen cases there is no note concerning the temperature. In the other thirty-two cases the temperature was normal seven times (21.87 per cent.). In eight cases (25 per cent.) fever is stated as occurring, in two cases (6.25 per cent.) it occurred at times, in three cases (9.38 per cent.) it was intermittent while in eleven cases (34.37 per cent.) it was a septic type with evening exacerbations. In one other case the temperature was subnormal.

Blood.—A note on the blood was found in twenty-six instances. It was normal nine times (34.61 per cent.), anemic eleven times (42.30 per cent.), and polycythemia occurred six times (23.08 per cent.). The anemia was not marked in any instance, the lowest red count being 3,200,000. Increase of red blood-cells was very striking in several instances and reached 7,000,000 in one and 8,200,000 in another. In the latter case the white blood-cells were also increased, 31,428. As a rule the white blood-cells were not increased, and their variations seem totally independent of the number of red blood-cells.

Skin.—A note on the skin occurred only nineteen times. It was said to be normal in color in two cases (10.5 per cent.), pale in seven (36.84 per cent.), earthy in one (5.3 per cent.), purpura and ecchymoses each occurred once, icterus twice, and cyanosis five times (26.3 per cent.).

Result—Thirty-four of the cases were discovered at autopsy, the remaining seventeen at operation Of these seventeen, ten patients (58 8 per cent) recovered, five died (one four and one-half months after operation), and in two the result is not stated

ANATOMICAL EVIDENCE OF TUBERCULOSIS

Spleen—Weight The weight varied greatly, the lowest weight was 150 gm , in a 14½-year-old girl reported by Lefas, while the highest was 3,780 gm in the case of Rendu and Widal The following tabulation will show the weight in thirty-one cases in which it was recorded

No of Cases	Gm	No of Cases	Gm
8	150- 500	7	1,500-2,000
5	500-1,000	2	2,000 3,000
6	1,000-1,500	3	3,000 4,000

Appearance While the appearance of the spleen was very varied, the limited space in the table allows only a few words, and since the pathology of the various types of the disease will be discussed at length below, it will suffice here to say that in all but four cases the spleen was the seat of either tubercles of varying sizes or large caseous masses Of these four the cases of Cominotti and Delore showed only a great enlargement of the spleen and extensive fibrosis In neither case is the evidence absolute that the spleen was the seat of a tubercular process In Coley's case the spleen was not only much enlarged but also showed numerous hemorrhages The only evidence that it was tubercular is in the title of the author's communication In Hamilton's case there was a large cyst which proved microscopically to be a broken-down tubercle

Of the positive cases, fourteen showed tubercles which were for the most part conglomerate, while twenty showed numerous large caseous masses which in several instances attained the size of an orange In one case there were hemorrhages and tubercles, while in three cases there was not only extensive tuberculosis but also fibrosis Of the fifty-one cases the gross appearance was more or less characteristic in thirty-nine, doubtful in three and not mentioned in nine

In the analysis of the findings in the liver, lymph-nodes, etc , to follow, it will be necessary to bear in mind that only thirty-four of the cases came to autopsy

Liver—In eighteen instances (35 28 per cent) there is no note on the liver, only three of these were autopsy cases, of the remaining thirty-three, nine (17 64 per cent) showed normal livers and twenty-four (47 per cent) showed positive evidence of tuberculosis of the liver

Lymph-Nodes—In twenty-three instances no mention is made of the lymph-nodes, six of these were autopsy cases In twelve cases with autopsy the glands were uninvolved, while in sixteen they were involved mesenteric ten times cervical three times bronchial twice splenic once

Lungs.—There are twenty-one cases in which no note on the lung is found, three of these were autopsy cases. The lungs were negative in sixteen instances. Calcified nodules occurred six times, and definite tuberculosis nine times, in several the involvement was extensive. In five the evidence that the pulmonary involvement was secondary seemed to be conclusive.

Elsewhere.—In nineteen cases including three autopsies there was no mention of tuberculous involvement of any other organ. Of the remaining thirty-three cases, eleven were negative, in eight the peritoneum or omentum was involved, the vertebræ in one, the mitral valve in one etc. The tuberculosis of the spleen was the only involvement found at autopsy in only one instance (Scharold), while the disease was confined to the spleen and liver three times (Brute, Romanow and Bruns).

Tubercle bacilli were looked for in twenty-four of the fifty-one cases. Of these twenty-four, seventeen were positive and only seven negative.

SUMMARY

There are fifty-one cases of so-called primary tuberculosis of the spleen included in the above table, beside these, several others, which were inaccessible, are omitted except for reference. The large number of observations make it necessary to alter the conclusions of other writers in many respects, but without going into these differences which only occur as a result of a more complete survey of the literature, the table may be briefly summarized as follows:

So-called primary tuberculosis of the spleen occurs most frequently between the ages of 20 and 40, but may occur at any age, the limits being 1 year for the youngest and 80 years for the oldest individual.

It is equally distributed between males and females.

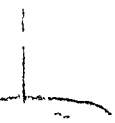
The onset of the disease is characterized either by pain or tumor or both in the splenic region (over 70 per cent.). In a few instances these symptoms are associated with gastric or respiratory disturbances, loss of weight, weakness or lassitude. These cases, as a rule, have a chronic course. In contrast to the above group there is another in which the symptoms of onset are much more striking and characteristic of an acute infectious process. These have the following symptoms-complex: collapse, fever, chills, backache, etc., and run an acute course. There remains still another group in which the symptoms of onset and the course are intermediary between the above two groups.

The blood picture is very inconstant. Both the red and white blood cells may be normal, increased or decreased.

The skin may be normal, pale, cyanotic, or icteric. Purpura or ecchymoses also may occur.

Death invariably follows if the spleen is not removed. In the cases in which splenectomy was performed, the results are remarkable, 59 per cent. recovered.

?	Purpu	?	
emia	Ecchym	?	
?	Pale	?	No microscopical notes
?	Cyano	?	Death seventeen days after onset
ative	?	?	Author refers to a similar condition in child's sister
00, W 6 000	Cyano	Negative	Author thinks the hepatized right lung was probably tuberculous
0, W 31,428	Earth	Negative	
0, W 6,000	?	Positive (sections)	Symptoms obscure by phlebitis of left leg
?	?	Positive (pigs and sections)	Patient had been operated on for glands of neck previously
mal	?	Positive (pigs)	Author thinks the pulmonary involvement probably due to direct extension through the diaphragm
?	Cyano	Positive (pigs)	Authors think the lung lesion probably primary
0, W 5,000 to 65 per cent	Cyano	?	
?	?	?	Author says "In other parts of body the tubercles also showed a tendency to grow to an unusual size
?	?	Positive (pigs)	
?	?	Positive (in sections)	Splenic tumor discovered accidentally
?	?	?	
?	?	Positive (sections)	
?	?	Positive (in vegetations)	It is interesting to note the presence of tubercle bacilli in the heart's blood
?	?	?	Patient entered the hospital to be treated for a cough
?	?	Negative	Author thinks lesion of spleen not secondary to those of lungs
?	?	?	
mal	?	?	Tuberculin test was positive
?	?	Positive (sections)	
00, W 12 000	Pale	?	
nemia	?	?	No microscopical notes
?	?	?	The author insists on tuberculosis of the spleen being primary in this case
?	?	?	Authors think the process began in the glands and that here and in the spleen the process was chronic
?	Subject	Negative	
00, W 2,200	Negat	?	
?	Cyano	Positive	
00, W 4,800, per cent	Pale	?	
00, W 1,860, per cent	?	?	
00, W 8,800, per cent	Pale	?	
00, W 5,400, per cent	Icter	Positive	
nemia	?	?	
?	?	?	Grawitz does not think the evidence of tuberculosis positive (See Reinhold)
?	?	?	Death three months later
?	?	Positive	Organ sewed to abdominal wound and drained
ormal	?	Positive	
?	?	Positive (sections)	
000, W 6,300	Pale	Positive (pigs and sections)	Cervical adenitis as a child, at the age of 11 and one month after operation
000, W 6 000, per cent	?	?	Patient gave birth to two children after operation
?	?	?	Pregnant one year later, condition good
000, W 7 825, per cent.	Negat		
000, W 7 500, per cent	Pale	Negative	
000, W 4,486	?	?	
000, W 6 600, per cent	?	Negative	
?	?	?	
000, W 7 500, per cent	Pa	Positive in pigs and sections	Splenectomy not possible because of adhesions
000, W 5,000, Hb ?	?	Positive (in sections)	Patient operated on for ventral hernia one year later
		Negative	peritoneum normal Author considers the nodule in the lungs as the pri



The spleen may be tremendously increased in size and weight In the majority it weighs between 1,000 and 2,000 gm

It may be studded with miliary or conglomerate tubercles or with large caseous masses even as large as an orange These may soften and leave cysts lined with caseous material, or they may be partly or completely healed

In 80 per cent of the cases in which the liver was examined it showed tuberculosis In 57 per cent of the cases in which the glands were examined, more or less tubercular glandular involvement was found

In 40 per cent of the cases examined the lungs showed evidence of tuberculosis In 16 per cent there were healed nodules, while in 24 per cent the process was still active

Tuberculosis was found elsewhere in 66 per cent of the cases Only one case showed the tuberculosis to be confined to the spleen and in three cases, only the spleen and liver were involved

CLASSIFICATION

Various classifications have been suggested from time to time by different authors, most of which are based on the distribution of the tubercular processes in the body The following one, first emphasized by Collet and Gallivarden, and later by Block, Palumbo, and Lefas, remains the most satisfactory These authors divided the cases into three groups (1) splenic (2) spleno-hepatic, (3) spleno-hepato-glandular The names in themselves are sufficiently explanatory and simply indicate the organs involved by the process There are cases which belong to each type Scharold's case is the only one in which the evidence is sufficient to include it in Group 1, and the cases of Brute, Romanow and Bruns may be included in Group 2 The case of Courmont, Tixier and Bonnet and our own case are instances of Group 3

There remain, then, the vast majority of cases which do not strictly conform to any of the three types suggested by Colet and Gallivarden The more carefully one searches, the fewer cases will belong to Group 1 and Group 2 and the more to Group 3 Any anatomical classification would be somewhat unsatisfactory, and since all the types above described may run either an acute, subacute or chronic course, it seems that it would be of advantage to divide the cases into these three forms

Acute Type—The acute cases are so few in number and have been so little emphasized that a short abstract of a few typical instances will be given

Scharold's case was that of a healthy convict who was suddenly seized with symptoms suggesting an acute overwhelming general infection There were high fevers prostration headache, cough epistaxis diarrhea retention of urine, delirium and general cyanosis The spleen was

greatly enlarged Death occurred on the seventeenth day Necropsy showed a tuberculosis limited to the much enlarged spleen

Stewart's patient was a nurse who took charge of a man, ill of tuberculosis, three weeks after she had recovered from an attack of grip Within two weeks she became ill with chills, fever and backache, and her illness terminated fatally on the sixty-eighth day On the first examination, ten days after onset of the illness, the spleen was markedly enlarged The chest was negative until two weeks before death, when fine râles became evident in both lungs On the thirty-sixth day two nodes were palpable in the left supraclavicular fossa and on the fifty-eighth day there was evidence of meningeal involvement The autopsy showed massive tuberculosis of the spleen diffuse miliary tuberculosis of the liver and lungs, caseous supraclavicular lymph-nodes and tubercular meningitis While Stewart could not demonstrate that the infectious process was limited to the spleen in its early course yet he believed that it was fair to assume this in view of the symptomatology and history of the case

These two cases will suffice to illustrate the clinical aspects and course of the small group of acute cases

The subacute cases are likewise rare, and in order to illustrate them more clearly the following observation may be cited The report will be detailed, since it was the inspiration of the paper and has not been previously recorded

CASE REPORT

History—J W P Medical No 27,566 White male, aged 34 entered the service of Dr Barker June 24, 1911, complaining of fever He had had the usual diseases of childhood (measles mumps, whooping cough) which ran uneventful courses and were not followed by any complications Eleven years before admission he had an attack of asthma which lasted about one month

The present illness began in October 1910, about nine months before admission It was characterized by attacks of lassitude chilliness fever loss of appetite, pain in the back and joints of the legs, and jaundice These attacks lasted from a week to twelve days and were of increasing severity

Physical Examination (Dr Clough, June 28)—The patient is very sparsely nourished and shows marked loss of weight The scleræ are slightly jaundiced, the skin of the entire body is sallow and pale, there is marked enlargement of the cervical glands on the right, especially those on the outer end of the clavicle which vary from 5 mm to 2 cm in size They are discrete, not tender, firm and not adherent to the skin or underlying tissue The submaxillaries are just palpable, also the epitrochleais and axillaries Inguinals are not enlarged

Thorax The left clavicle is slightly more prominent than the right The right side moves more freely than the left The percussion note is a little shorter just below the left clavicle There is a little prolongation of expiration above and below both clavicles, particularly on the right No râles are heard The percussion note is a little less resonant in the right supraspinous fossa and also opposite the fifth spine on the right There is no special change in the breath sounds

The heart is not enlarged The sounds are clear except for a soft systolic blow which is not transmitted and is loudest at the base

The abdomen is a little full, especially in the epigastrium There is no tenderness The liver edge is not felt The dulness reaches the costal margin The spleen is easily felt, reaches 5 cm below the costal margin and is very firm

Dr Clough concluded that the condition was one of the following the first being the most likely

1 Tuberculosis of the lymph-nodes and fibrous lesions of the left apex 2 Hodgkin's disease 3 Estivo-autumnal malaria 4 Lues

On June 27 Widal and Wassermann reactions were negative, the red blood-cells 3,800 000, white blood cells 5,400, hemoglobin 55 per cent (Sahli) The differential count was as follows

Polymorphonuclear neutrophils 81 per cent
Polymorphonuclear eosinophils 5 per cent
Lymphocytes 15 per cent
Large mononuclears 2 per cent
Transitionals 1 5 per cent
No parasites are to be made out

Examination of stools and ophthalmoscopic examination negative Calmette tuberculin reaction negative Blood-culture negative

On July 1 the following note was made by Dr Futcher Fever of a continuous type The patient is very sallow, almost the color of a patient with pernicious anemia The conjunctivæ have a distinct icteric tint, and the skin of the entire body is icteric There is no general glandular enlargement There is, however, a group of enlarged glands in the right supraclavicular fossa which vary from 1 to 2 cm in diameter The liver dulness extends 2 5 cm below the costal margin At this point the edge is indistinctly felt The spleen is distinctly enlarged, firm and the edges are felt, with the patient on the right side, 4 cm below the costal margin Examination of fresh blood shows a moderate grade of pallor of the individual red cells, with a striking variation in size (microcytes and macrocytes), much poikilocytosis and a marked leukopenia No malarial parasites are seen after a prolonged search Impression enlarged glands on the right side of the neck with a history of recurrent attacks of continuous fever, anemia and leukopenia suggest very strongly Epstein's ruckfallsfieber of Hodgkin's disease Acute miliary tuberculosis and malignant disease must be kept in mind

The report of the *x*-ray examination was mediastinitis and infiltration of right lung and left upper

Treatment—On June 30 the patient was put on quinin gm 1 30 (gr 20) three times a day after meals His temperature, which was then 104 5 F, slowly fell and reached 99 F July 3 The patient felt better and was brighter

Biopsy—July 14, a small node was removed from the neck The following pathological report was made by Dr Winternitz The gland shows a diffuse granulation tissue about the periphery This is not very vascular and contains numerous fibroblasts and mononuclear cells These areas tend to form whorls and show many cells similar to epithelioid cells Toward the center the section becomes more cellular and small whorls show caseous centers Epithelioid cells are common but no giant cells are to be seen Two guinea pigs inoculated with an alkaline solution of sodium hypochlorate (antiformin) extract of part of the gland died within ten days and showed no lesions *Diagnosis chronic inflammation* probably tubercular

Following the quinin the patient's temperature remained normal for five days and again rose on July 10 to 103 F It remained elevated varying from 102 to 104 8 F Quinin in the same doses as had been given previously had no effect on the temperature The patient's condition gradually grew much worse He died July 26 1910, at 2 a m

Necropsy—The necropsy was performed at 9 a m July 26 Autopsy No. 3576 Anatomical diagnosis Healed apical scar, tuberculous lymphadenitis massive tuberculosis of spleen healed healing and fresh tubercles of liver anemia, emaciation jaundice acute pleurisy pleural and peritoneal effusion

The body is that of a much emaciated white man 175 cm long The skin is loose and of a yellowish hue The conjunctivæ are yellow The lymph nodes of the neck are large discrete and firm especially over the right clavicle The

abdominal cavity contains about 400 c c of a deep yellow, bile stained fluid The liver extends 3 5 cm below the tip of the ensiform, and reaches the costal margin in the mammillary line Both pleural cavities contain about 200 c c of fluid, similar to that in the peritoneal cavity The thymus is large and fatty It, together with a mass of large, firm, elastic, but discrete lymph nodes fills the anterior mediastinum

Heart shows one fibrous adhesion attaching the apex to the parietal pericardium Otherwise it shows nothing of particular interest

Lungs—The left pleural surface is dull and granular At the apex of the upper lobe there is a large area 3 cm in diameter of thickening involving the pleural and subpleural portions A few fibrous strands extend into the lung tissue The hilic nodes are slightly enlarged, one measures 3 cm It is discrete, slightly elastic and firm On section it is striated, with bands of ivory white, semi-translucent tissue, which are separated by depressed areas of the same nature or rarely by small yellow, opaque zones

The right lung is similar to the left, and has an apical scar of the same nature

Spleen—The spleen measures 26 by 15 by 8 cm and weighs 1,350 grams It is bound down by a fresh, stringy, friable, grayish-yellow exudate which only partly covers the surface Through this the surface may be seen sprinkled everywhere with yellowish, opaque dots which vary in contour and size, the largest measuring only about 5 cm in diameter Some of them show reddish centers They are slightly elevated and firmer than the intervening pulp The hilic vessels are normal, but the vein is distended with blood The spleen is flabby On section the pulp is dark brownish or purple red and studded everywhere with nodules like those described on the surface These occupy as much of the tremendously enlarged gland as the pulp itself The malpighian corpuscles are not visible The fibrous tissue is not increased

The duodenum contains no bile In the ampulla is a small amount of mucus The ducts are otherwise patent Along the upper border of the pancreas are a large number of nodes running like a streamer from a mass of nodes near the receptaculum chyli These, as well as the enlarged lumbar nodes, have exactly the characteristic of the bronchial nodes above described The thoracic duct seems free of lesions

Liver—The liver measures 32 by 28 by 9 cm and weighs 2,850 grams Its capsule is glistening, but studded by gray nodules and diffuse, gray capsular thickenings On section its architecture is obscured In many places gray masses of semitranslucent, firm tissue run along the capsule These vary in thickness, in some places measuring only a few mm, while in other places they measure 1 cm Similar firm areas occur particularly around the portal vessels and are in places several cm wide The vessels are compressed and irregularly thickened along their intimal surface This is particularly true of the portal vein Beside these large, gray, translucent areas there are also irregular, opaque, yellow zones, with their periphery injected, scattered through the parenchyma These may be 1 cm in diameter or of decreasing size to those which are just on the point of visibility The lobulation of the liver is obscured greatly by these abnormal areas The parenchyma of the liver is pale, yellowish brown The gall bladder contains a dark, tarry bile

Microscopic Examination—Microscopically, some of the lymph-nodes have large areas of caseation surrounded by zones of cellular proliferation In others the surrounding tissue shows a diffuse necrosis involving most of the cells or there is an infiltration of cells into the gland These are large, often with lobed nuclei and sometimes multinucleated Many of these cells have large, pale nuclei with one or more deeper staining central nucleoli and resemble the giant cell in Hodgkin's disease, but in no instance is the similarity complete These cells are, in general, the various types of wandering cells found in inflammatory processes

The spleen is mottled by large caseous zones Here they are much less cellular than in the liver and are surrounded by only a small number of round or epi-

thelioid cells The sinuses of the spleen between these caseous masses are dilated and congested They contain many wandering cells and an occasional giant cell The malpighian corpuscles in many instances are converted into caseous masses The central artery is often still visible as a shadow and in the smaller nodules reach the capsule, where an exudate composed of fibrin, red blood-cells and mononucleai cells is seen

The liver is very extensively changed Throughout, small areas characterized by a central zone of coagulative necrosis and surrounded by epithelioid and mononuclear cells occur Many of these involve minute bile ducts and are consequently bile-stained in their centers Most of them do not attain any great size The larger nodules have an entirely different appearance They are composed of a granulation tissue rich in capillaries and mononucleai cells without any caseation Many of these border on large blood-vessels Occasionally a larger zone of caseation occurs in the center of such a fibrous zone In some areas the liver cells between the caseous masses have undergone necrosis and only remain as shadows, the connective tissue still remaining conspicuous In general the areas of caseation are far less conspicuous than the areas of granulation tissue, and in almost every instance the caseous nodule is surrounded by a mass of such granulation tissue In many instances this granulation has become quite fibrous The liver parenchyma not involved by this process is somewhat changed The capillaries are everywhere widened, and the liver cells are atrophic

CHRONIC FORM

The chronic cases are so numerous and form such a large bulk of the discussion of the foregoing table that they may be rapidly dismissed

The onset in these is insidious, beginning most often with indefinite pain, accompanied by a feeling of weight in the left hypochondrium This is associated with enlargement of the upper left abdomen Later there may be gastric symptoms, with loss of appetite and weight, or there may be dyspnea These symptoms may extend over a long period of time, twelve months or longer Fever may or may not be present Finally, after several years, as a result of enfeebled resistance, a general tuberculosis may ensue

PATHOLOGY

The pathology of the spleen in so-called primary tuberculosis does not differ essentially from what occurs in secondary tuberculosis There are three factors which must be considered — first, the general reaction of the spleen to the acute infection which manifests itself as an hypertrophy and engorgement, such as occurs in typhoid fever, second, the specific lesions of the tubercle bacilli and their localization, and third, the reparative processes of the tissue following the injury

It is evident that the more acute the process is, the more pronounced the first of these will be The actual lesion of the tubercle bacilli may be slight if the course of the disease has been very rapid As a rule however, the specific lesion of the tubercle bacillus is much more prominent The spleen in the acute cases is greatly enlarged, it is either firm and resistant, with a tense capsule, or more soft, and even diffluent It is studded with tubercles which may be invisible to the naked eye or as

large as 1 cm in diameter These shimmer through the capsule and are seen on section as yellow, opaque masses surrounded by a hemorrhagic zone They may be blood-stained or softened in their center The splenic pulp is engorged and in excess

Microscopically the tubercles show extensive necrosis and have much nuclear débris in their center They may be surrounded by a small number of round cells or epithelioid cells or simply by the engorged splenic pulp Giant cells are very scarce The sinuses of the pulp are engorged with blood and contain many leukocytes and phagocytes laden with débris Some of these may show division The malpighian corpuscles are scarce, many of them are the seat of caseous masses, in which the central artery may still be evident There may also be a small peripheral zone of lymphocytes

When the reparative process is more evident, as occurs in the less overwhelming infections, the hypertrophy of the spleen may be less marked and the more specific lesions of the bacteria and the reparative process more definite The spleen is enlarged, red and of a fairly firm consistence On section the pulp is in some excess the caseous areas are less evident and are replaced by firmer, more shotty, semitranslucent nodules with opaque, yellow centers These nodules show microscopically central caseation with a definite peripheral zone of epithelioid and round cells Giant cells are much more abundant and the changes in the pulp much less marked

In the still more chronic forms the healing process vies with the activity of the tubercle bacillus for first place, and the result is a sclerocaseous process The spleen is very voluminous, its upper pole is often bound down by adhesions due to a perisplenitis The surface may be rough, with yellowish prominences that vary from the size of a pea to that of a walnut On section the organ is very firm and indurated, caseous masses of varying sizes and fibrous bands are visible in the grayish-brown pulp Some of the masses are yellow, opaque and firm, and surrounded by a grayish, more translucent zone, while others are much softer, almost diffluent and have a cinder-gray color It is these latter nodules which may become cystic by absorption of their softened centers Microscopically the capsule of the spleen is thickened and composed of dull, fibrous tissue of a hyaline appearance Similar fibrous bands run into the splenic pulp and contain caseous masses within them The extent of these two processes — the fibrosis, on the one hand, and the caseation on the other — varies within wide limits, usually in inverse proportion The caseous masses contain some nuclear débris in their center and are surrounded by epithelioid cells, round cells, giant cells and fibrous tissue The pulp is also profoundly altered The reticulum is greatly thickened composed of dense bands of adult fibrous tissue, between which there are only a few white cells In short, the pulp is converted into an areolar

fibroid tissue the spaces of which are full of blood Here and there an islet of white blood cells or of more advanced sclerosis occurs Most of the malpighian corpuscles have disappeared Infarcts too may occur as a result of extensive hemorrhage

DIAGNOSIS

In the more acute cases the diagnosis is the most difficult The history, the presence of a tubercular lesion elsewhere, an enlarged spleen and liver, with tenderness in the left hypochondrium, the character of the fever, the occurrence of polycythemia or cyanosis, or both, and the tuberculin reaction, are the guides In the more chronic cases, the presence of the above factors plus an enlarged spleen and liver and the absence of a leukemic blood picture are of importance

Polycythemia with cyanosis in relation to tuberculosis of the spleen was first emphasized by Rendu and Widal Their report was followed within a few days by that of Moutard, Martin and Lefas In their case polycythemia without cyanosis occurred and simultaneously with the latter report appeared the one of Achard and Castaigne wherein it is stated that neither polycythemia nor cyanosis had been present This has been the subsequent experience and while the presence of polycythemia or cyanosis may be a help in diagnosis, the fact that they may occur in other diseased conditions of the spleen and may be absent in massive tuberculosis of this organ, renders their value limited Progressive leukopenia may occur as in our case This, too, may be of aid in the locating the disease in the spleen

The fever usually runs a septic course, but as in the case of Palumbo our own and others, it may be remittent in character and closely resemble the *Pel-Epstein-Rückfallsfieber* described for Hodgkin's disease

The tuberculin reaction has been used in so few cases that its value cannot be stated *It should be tried by all means* though in our case the Calmette reaction was negative

TREATMENT

Primary tuberculosis of the spleen, whether acute or chronic is an absolute indication for splenectomy Even though the process may have reached the liver, as it does in most cases, or the lymph-nodes it is probable that these organs might be able to successfully cope with the process were they not being fed tubercle bacilli constantly through the portal circulation

Finally, there are two points which deserve a word of comment First, in so many instances in which there has been a careful autopsy pulmonary scars, old cervical adenitis etc have been found that the conclusion becomes evident that the process in the spleen is most often secondary to some old healed or quiescent focus Still there are cases such as the

one reported by Bruns, in which despite a careful search with the above point in view, no lesions except those in the spleen and secondarily in the liver could be demonstrated Bruns feels, therefore, that an actual primary tuberculosis of the spleen is possible The fact that tubercle bacilli may be present in the blood in a state of absolute rest, and that there may be no specific lesions of the viscera for a long period may explain this case Such instances, however, are exceedingly rare, as are also cases of the type Bruns reports, and as a rule the involvement of the spleen is secondary, even though the primary lesion may be very inconspicuous The prevalence of this special form of tuberculosis in adults speaks in favor of a secondary or more probably a tertiary involvement, due to an auto-infection [4]

Secondly, there remains the question how a massive visceral tuberculosis such as has been described may remain localized in the spleen for such a long period without disseminating itself throughout the viscera It is possible that the very localization of the process may have decreased the likelihood of dissemination The case of Ferrand and Rathery is of interest in this respect At autopsy there was a massive tuberculosis of the spleen, but all the other organs were free of tuberculosis except for an acute tubercular endocarditis Tubercle bacilli could be readily demonstrated, both in the vegetation and in the heart's blood Still there were no lesions of the viscera This explanation, however, may only be applied to the rarest cases, and for the most part we have to deal with a relatively much greater distribution of the disease, affecting particularly the liver and lymph-nodes Courmont, in the discussion of his case of tuberculosis of the spleen and lymph-nodes, considers that the localization of the disease may be explained in part by the low virulence of the bacteria and that the attenuation may have adapted it in some way to these special tissues He inoculated guinea-pigs with pieces of the gland and these animals slowly developed an abnormal involvement of the lymph-nodes, while the animals inoculated with the meningeal exudate died in a much shorter time of a general tuberculosis This observation is of particular interest and seems to lend support to the theory that various tissues of the body in some way are capable of modifying the action of the tubercle bacillus The recent work of Liebermeister[5] is of interest in this respect He could not demonstrate that tubercle bacilli obtained from one organ tended to bring about lesions of this organ when injected into rabbits On the other hand, he showed definitely that when the bacilli were injected into the circulation, certain organs namely, lung, liver, iris lymph-node, etc, were involved in the order named, and what is of most

4 See Pirquet's division into primary, secondary and tertiary tuberculosis Allergy, ARCH INT MED, 1911, vii, 403

5 Liebermeister Beitr z pathol Anat u allg Pathol, 1911, l, 398

interest, the lesions were most malignant in the lungs and most benign if these terms be permitted, in the liver These results confirm the findings of tuberculosis in man There are such organs as the lungs which, first, are exceedingly prone to the infection, and in which, secondly, the process usually develops rapidly They are such organs as the liver which are also prone to the infection, but where the process is, as a rule, rapidly healed, and lastly, there are organs, such as the thyroid, pancreas and muscle, which are rarely affected Our own case is a striking illustration of the second group Here the tubercle bacilli were fed to the liver in large quantities, and while the lesions were extensive, most of them were the result of healing of the tubercular foci

The predilection of certain germs to manifest their specific lesions in definite tissue, while neighboring tissues may remain unaffected, is so widespread and well recognized that it suggests the possibility that specific tissues may have some type of resistance to specific bacteria This is confirmed to a certain extent by the recent work of Levin,[6] who concludes from his experimental injections that the reason carcinoma forms metastases in lymph-nodes is not due to differences in the channels of transportation in carcinoma and sarcoma, but due to the specific affinity between carcinoma cells and the cells of lymphatic tissue

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6 Levin Jour Exper Med, 1911, xiv, 148

STUDIES OF MALARIA IN PANAMA IV RELATION OF MALARIA TO OTHER DISEASES WITH ESPECIAL REFERENCE TO DYSENTERY*

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LOS ANGELES

This study was begun with the idea of examining data bearing on the so-called dysenteric type of pernicious malarial fever The study naturally extended itself until it included besides the malarial fevers the six largest groups of disease met with in Panama, namely, acute dysentery, amebic dysentery, typhoid fever pneumonia, pulmonary tuberculosis and chronic nephritis The statistics that will be given cover the years 1908 and 1910 during which the records of the hospital are most complete

Among eighty-eight cases of pernicious malarial fever that occurred in Colon Hospital from November, 1907, to May 1910, thirteen patients had diarrhea, usually slight, and twenty patients were constipated The remaining fifty-three patients showed no intestinal disturbance All patients were given as routine 3 grams of calomel on the evening of admission and 2 ounces of a half saturated solution of magnesium sulphate the following morning The slight diarrhea noted in a few cases was not in excess of what might be accounted for by the purgatives It is safe to say that without purgatives a great majority of the patients would have been badly constipated In not a single instance were there dysenteric phenomena — diarrhea, tenesmus, and stools containing blood and mucus I have observed, also many other pernicious cases in Panama which are not included in this series, and I have seen neither the "choleraic" nor "dysenteric" types, although I have watched for them carefully The intensity of infection in the pernicious cases has varied all the way up to a 66 per cent infection of the red corpuscles in the peripheral blood

I may say at once, then, that the "choleraic" and "dysenteric" types of pernicious malarial fever have not occurred in my experience in Panama and I know of no such cases in the literature in which coincident bacillary dysentery or other intestinal bacterial infections have been excluded by bacteriological examinations of the dysenteric stools The mere presence of many malarial parasites in the intestinal capillaries of

*From the Medical Clinic of Colon Hospital, Cristobal, Canal Zone
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‡Manuscript submitted for publication March 11, 1912

TABLE 1.—CONDITIONS COMPLICATING MALARIAL INFECTIONS BY MONTHS FOR 1908 AND 1910

Date	E A*	Tei T	Acute Dys	Acute Dys and E A	Acute Dys and Tei	Amebic Dys	Amebic Dys and E A	Amebic Dys and Tei	Typhoid	Typhoid and E A	Typhoid and Tei	Pneumonia	Pneumonia and E A	Pneumonia and Tei	Tb pul	Tb and E A	Tb and Tei	Nephritis chi	N and E A	N and Tei
1908																				
January	132	54	6	1	0	14	2	0	7	0	1	21	1	0	18	1	1	7	1	1
February	74	34	7	4	1	6	1	0	6	1	1	15	0	1	12	5	2	8	1	0
March	62	36	8	2	0	6	0	0	11	1	0	11	1	0	9	1	0	8	0	0
April	84	36	5	0	0	8	2	0	5	0	2	13	0	0	8	0	0	5	1	0
May	42	27	2	1	0	10	0	1	2	0	0	18	1	1	13	0	0	16	1	0
June	66	25	4	0	0	4	0	1	3	1	0	27	1	0	10	0	0	18	1	1
July	354	73	4	0	0	6	1	0	6	0	0	13	2	0	14	1	0	14	3	0
August	402	70	5	1	0	12	1	0	2	0	0	4	1	0	25	2	0	6	0	0
September	321	69	5	1	0	9	4	1	10	1	1	9	1	1	10	2	0	12	4	1
October	526	56	5	3	0	9	4	1	7	1	1	9	1	0	22	4	0	7	1	0
November	279	26	7	3	0	14	9	0	6	4	0	9	2	0	21	4	0	10	4	0
December	147	26	6	2	0	20	4	1	2	2	0	7	1	0	28	9	0	10	5	0
	2,489	532	64	18	1	118	28	5	67	11	6	156	12	3	190	29	3	121	22	3
1910																				
January	44	11	16	2	1	5	0	0	3	1	0	4	1	0	17	1	0	10	1	0
February	30	9	8	1	0	2	0	0	2	0	0	5	0	0	10	0	0	4	0	0
March	29	11	9	0	0	3	0	0	3	1	0	1	0	0	16	0	0	7	0	0
April	59	18	9	1	0	1	0	0	4	0	1	7	0	0	18	1	0	18	2	0
May	57	12	1	0	0	1	0	0	5	0	0	6	1	0	23	1	0	13	1	1
June	298	13	10	0	1	4	0	0	3	0	0	11	0	0	10	0	0	5	1	0
July	356	34	12	4	0	1	0	0	1	0	0	12	0	0	10	0	0	12	6	0
August	277	38	14	3	0	3	1	0	6	0	0	9	1	0	12	1	0	19	4	0
September	116	10	9	1	1	8	1	0	7	0	0	9	0	0	17	1	0	8	1	0
October	52	17	1	0	0	0	0	0	6	0	0	5	1	0	14	0	0	7	1	0
November	19	6	9	2	0	1	1	0	4	0	0	6	0	0	11	0	0	8	0	0
December	51	13	3	0	0	0	0	0	2	1	0	13	1	0	5	1	0	11	0	0
	1 118	252	101	14	3	32	3	0	46	3	1	88	5	0	163	6	0	122	17	1
Total	3 607	784	168	32	4	150	31	5	113	14	7	244	17	3	353	35	3	243	39	4

*E A—estivo autumnal malarial parasites. Tei—tertian

certain dysenteric patients is not sufficient evidence to prove that the dysentery was of malarial origin The dysentery itself, as will be shown later, probably tends to cause an exacerbation of a latent malarial infection Thirty-nine of our eighty-eight patients with pernicious malarial fever died and practically all of them were examined post mortem In none was there any evidence of enterocolitis

On the other hand, a small percentage of both estivo-autumnal and tertian malarial infections of mild or moderate intensity have been complicated by acute dysentery Likewise a small percentage have been complicated by amebic dysentery, typhoid fever, pneumonia, pulmonary tuberculosis and chronic nephritis

Table 1 represents the number of these complicating infections by months for the years 1908 and 1910 In connection with it, it is interesting to note that during the year 1908, 28 32 per cent of the employees of the Isthmian Canal Commission were admitted to the hospitals with

TABLE 2.—SHOWING THE PERCENTAGE OF MALARIAL INFECTIONS COMPLICATED BY OTHER DISEASES

	Total	Acute Dysent		Amebic Dysent		Typhoid Fever		Pneumonia		Tuberculosis		Nephritis	
	No Cases	No Cases	Per cent	No Cases	Per cent	No Cases	Per cent	No Cases	Per cent	No Cases	Per cent	No Cases	Per cent
Mal E A	3 907	32	82	31	79	14	36	17	44	35	90	39	1 00
Mal Ter	784	4	51	5	64	7	89	3	38	3	38	4	51

malarial fever, while during 1910 only 18 6 per cent were admitted[1] That is, the number of malarial infections in 1910 was almost exactly two-thirds of the number in 1908 The effect of this difference on the frequency of complications is striking

For purposes of analysis it is necessary to construct subtables from Table 1

Malarial infections were complicated by the above diseases in such a small percentage (1 per cent or less) of instances that it is impossible to think that malaria was concerned with the onset of any of them Furthermore, there is no striking difference in the relative percentages, as there should be if malaria were an etiologic factor in any one The percentage of complications by acute dysentery[2] is practically the same

1 Gorgas, W C Report of the Department of Sanitation of the Isthmian Canal Commission for the month of January, 1911

2 Recent bacteriological studies conducted at Colon Hospital indicate that most of the cases of acute dysentery are due to *B dysenteriæ* (Shiga and His Y)

as by amebic dysentery The table does not yield the slightest evidence that malaria predisposes to any of the complicating diseases included in the tables

TABLE 3 —SHOWING THE PERCENTAGE OF OTHER DISEASES COMPLICATED BY MALARIA

Disease	Total No	E A		Ter		Corrected Ter	
		No	Per cent	No	Per cent	No	Per cent
Acute Dysentery	168	32	19 0	4	2 4	20	12 0
Amebic Dysentery	150	31	20 6	5	3 3	25	16 7
Typhoid fever	113	14	12 4	7	6 2	35	31 0
Pneumonia	244	17	7 0	3	1 2	15	6 2
Tuberculosis	353	35	10 0	3	0 9	15	4 2
Nephritis	243	39	16 0	4	1 6	20	8 2

The column "corrected tertian" indicates what would have been the tertian complications if the number of tertian infections (784) had been equal to the number of estivo-autumnal infections (3,907)

In order to interpret Table 3 it is necessary to estimate the chance of coincident infections of malaria and the other diseases This would be simple, given the population drawn from, if all the infections had occurred at the same time, or if all had continued throughout the two years For instance, suppose the population drawn from to be 15 000 Of this number 168, or 1 12 per cent, had acute dysentery, and 3 907 had estivo-autumnal malaria Then 1 12 per cent of 3,907 would indicate the number of estivo-autumnal infections that would probably be complicated by acute dysentery, that is, about forty-four cases But all the infections did not occur at the same time They were distributed as shown in Table 1, throughout the years 1908 and 1910 In order to obtain the true rate of coincidence, therefore, it is necessary to calculate the chance of synchronous infection for each month in the two years Table 4 shows how this was done to obtain the number of infections that might be attributed to coincidence in the case of estivo-autumnal malaria and acute dysentery The population that Colon Hospital drew its patients from in 1909 was approximately 16,000, in 1910 13 500

Coincident infections of estivo-autumnal malaria and acute dysentery could be expected, then, in only about two instances It is unnecessary to present a similar table for each of the diseases studied but such a table for each has been worked out The results are given in Table 5

TABLE 4.—SHOWING CHANCE OF COINCIDENT INFECTIONS OF ESTIVO AUTUMNAL MALARIA AND ACUTE DYSENTERY

Date, 1908 Population 16 000	Cases of Acute Dysentery	Proportion of Population Having Acute Dysentery	Cases of E. A. Malaria	Number of Coincident Infections Calculated
January	6	00038	132	050
February	7	00044	74	033
March	8	00050	62	031
April	5	00031	84	026
May	2	00013	42	006
June	4	00025	66	017
July	4	00025	354	089
August	5	00031	402	125
September	5	00031	321	099
October	5	00031	526	163
November	7	00044	279	123
December	6	00038	147	056
Total number of coincident infections to be expected in 1908				798
1910, Population 13,500				
January	16	00119	44	052
February	8	00059	30	018
March	9	00067	29	019
April	9	00067	59	040
May	4	00030	57	017
June	10	00074	298	221
July	12	00089	356	317
August	14	00104	277	288
September	9	00067	116	078
October	1	00007	52	004
November	9	00067	49	032
December	3	00022	51	011
Total number of coincident infections to be expected in 1910				1 097
Total number in 1908 and 1910				1 895

TABLE 5.—SHOWING THE CHANCES OF COINCIDENT INFECTIONS OF ESTIVO AUTUMNAL MALARIA AND OTHER DISEASES IN 3 907 CASES

Complicating Disease	No. of Cases of Complicating Disease	Calculated Coincidence of Infection	Real No. of Synchronous Infections
Acute dysentery	168	1 895	32
Amebic dysentery	150	1 888	31
Typhoid fever	113	1 295	14
Pneumonia	244	2 484	17
Tuberculosis	353	4 135	35
Nephritis	243	2 646	39

This table is not exactly accurate It assumes that the infections of each month occurred at the same time during the month or that each infection lasted throughout the month This is an assumption of course not strictly true, especially in the chronic diseases, tuberculosis and nephritis, which, for purposes of discussion may be assumed to last a year Calculating from this as a basis, the number of coincident infections of estivo-autumnal malaria with tuberculosis would be about forty-nine with chronic nephritis, about thirty The calculated number of coincident infections of estivo-autumnal malaria with tuberculosis and nephritis approximately equals the real number of synchronous infections if I may use the word "infection" in connection with nephritis

But the real number of synchronous infections with the other four diseases cannot be accounted for by chance That malaria cannot be held responsible for the onset of any of the diseases has been shown by a study of the pernicious malarial cases and by Table 2 The alternative is that the diseases, acute dysentery, amebic dysentery, typhoid fever and pneumonia, cause an exacerbation of latent malarial infections, and this is probably the true explanation A large proportion of the population served by Colon Hospital has had malaria, and we may infer from our knowledge of malaria that in a considerable percentage of patients the infection was not entirely eradicated, that is, they still had a latent malarial infection If it is assumed that 18 per cent of the population had latent malaria, then 18 per cent of the 168 acute dysentery cases or thirty infections, would be superimposed on latent malaria [3] If these thirty latent malarial infections were "lighted up" by the dysentery and if one adds to them the two cases of calculated coincident infections, the number thirty-two is obtained, which is the exact number of real synchronous infections Of course this calculation is too exact to represent the truth of the matter, but I think that it indicates the true explanation of the combinations of malaria and the other diseases in Panama

If the explanation is correct, the interpretation of Tables 3 and 5 is clear Four of the diseases studied have a tendency to cause an exacerbation of latent malarial infections, and in the following order amebic dysentery, acute dysentery typhoid fever lobar pneumonia In the discussion following Table 5 it is concluded that tuberculosis and chronic nephritis probably do not have such a tendency and that the synchronous infections can be accounted for by coincidence

3 During the dry season of 1909 Darling determined the latent malarial rate in villages where no anopheles were breeding He found that 10 per cent of men who were at work without symptoms had parasites Among the families of Spanish and West Indian laborers the rate was 30 per cent The latent rate taken the year around must be much larger than Darling found it during the dry season and 18 per cent seems a conservative estimate (Darling S Jour Amer Med Assn 1909 liii 2051)

It is probable that this marked tendency of the dysenteries, causing a high rate of synchronous infection, furnishes an explanation of the common belief that malaria may itself cause dysenteric phenomena The effect has probably been mistaken for the cause

Additional evidence against the malarial origin of acute dysentery is found when one examines Table 1 by months In 1908, when the malarial rate was high the total number of cases of acute dysentery was only sixty-four, and 28 per cent of the cases were complicated by estivo-autumnal malaria On the other hand, in 1910 when the malarial rate was only two-thirds as high the number of cases of acute dysentery was 104 or two-thirds greater, and there were estivo-autumnal infections in only 13 4 per cent of the cases The number of cases of acute dysentery bears no relation, therefore, to the malarial rate, but the number of instances in which acute dysentery was complicated by malaria is in direct relation to the malarial rate, and, presumably, to the number of latent malarial infections

After the preceding part of this paper was written a patient with an estivo-autumnal infection was admitted to the hospital On the fifth day, when his temperature had reached normal, there was a sharp secondary rise and on the sixth day a sharp dysentery developed with pus blood and mucus in the stools We immediately made cultures on Endo's medium, from which we isolated *B dysenteriæ* (His Y) This case was evidently one of the rare instances of coincident infection due to chance for the dysentery did not precede the malarial fever and cause an exacerbation of a latent infection, but it developed at the beginning of malarial convalescence The dysentery subsided and the temperature was normal within three days This might easily have been considered an attack of malarial dysentery if cultures had not been made

CONCLUSIONS AND SUMMARY

1 The so-called "choleraic" and "dysenteric" types of pernicious malarial fever do not occur in Panama

2 In a study of 4,691 malarial infections it was found that the number of cases complicated by acute dysentery, amebic dysentery, typhoid fever pneumonia, pulmonary tuberculosis, and chronic nephritis was in each instance 1 per cent or less

3 Malarial infection appears to bear no etiologic relationship to acute dysentery or any of the above diseases

4 All the above diseases were complicated by a considerable percentage of malarial infections, the order of frequency being amebic dysentery, acute dysentery, chronic nephritis, typhoid fever, pulmonary tuberculosis, pneumonia

5 It is shown that the coincident occurrence of malaria with nephritis and tuberculosis is probably due to chance, while the synchronous

occurrence of malaria with acute dysentery, amebic dysentery, typhoid fever and pneumonia is chiefly due to a "lighting up" of latent malaria by the other diseases The two forms of dysentery have about equal power to determine an exacerbation of latent malaria, the influence of typhoid fever and pneumonia is only about one-third or one-fourth as great

I wish to thank Col W C Gorgas, Chief Sanitary Officer of the Canal Zone, for permission to use the material on which this paper is based

I am indebted also to Mr Hiram J Messinger, Actuary of the Traveler's Life Insurance Company of Hartford, Conn, for examining and confirming the mathematics of chance embodied in the paper

423 Security Building

STUDIES ON THE CIRCULATION IN MAN·

V EFFECT ON THE BLOOD FLOW IN THE HAND OF APPLYING DIFFERENT PRESSURES TO THE UPPER ARM, A CONTRIBUTION TO THE CLINICAL MEASUREMENT OF BLOOD-PRESSURE

G N STEWART

CLEVELAND, O

SECTION I THE INFLUENCE ON THE FLOW IN THE HAND OF A PRESSURE IN THE ARMLET EQUAL TO THE SYSTOLIC ARTERIAL PRESSURE

The question has been often discussed whether in the clinical measurement of blood-pressure the pressure regarded as systolic pressure is actually sufficient to obliterate completely the lumen of the artery or only sufficient, without obliteration, to block the passage of the pulse-wave, but scarcely, so far as I am aware, has it been conclusively answered I have put it to the test in the following way using three of the recognized methods of estimating systolic pressure, that is to say, the determination of the pressure at which the radial pulse first reappears after extinction (*a*) by palpation, (*b*) by the stethoscope applied to the brachial artery at the elbow, (*c*) by the graphic record of the Erlanger apparatus Broad armlets were employed

I first attempted to compare the heat given off by one hand during compression of the upper arm, by a known pressure in the armlet steadily maintained, with that given off by the other hand, in which the blood was circulating freely It is clear from the description of the method of estimating the blood-flow (Paper I) that for some time after complete cessation of the flow, the hand will continue to give off heat to the calorimeter since its interior is at a somewhat higher temperature than the calorimeter at the moment of introduction If the circulation is interrupted for a sufficient time, however the hand will eventually assume throughout its whole thickness the temperature of the calorimeter, and henceforth only the small amount of heat produced in the resting and asphyxiating hand will be given off If we calculate the blood-flow in the hand after complete interruption of the circulation from the heat given off by the hand

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*From the H K Cushing Laboratory of Experimental Medicine, Western Reserve University, Cleveland, O

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*Paper I of this series, containing a description of the method, appeared in Heart, 1911 iii 33, Paper II, Ibid p 76, Paper III, Am Jour of Physiol, 1911 xxviii, 133, Paper IV, Jour of Pharmacol and Exper Therap, 1911, ii, 477

TABLE I (EXPERIMENT 1) —SHOWING COURSE OF THE HEAT EXCHANGE WITH TOTAL INTERRUPTION OF CIRCULATION

Time	Calorimeter Temperature					From Beginning of Experiment				T—T′		H / T—T′		
	Actual		Corrected*			Increment of (corrected) temp		Heat Given Off						
	R	L	R	L	Diff	R	L	R	L	R	L	R	L	Diff
4 02	29 77	29 83			06									
4 03	29 89	29 93	29 90	29 94	04	13	11	454	384	6 92	6 87	666	567	10†
4 04	29 99	30 02	30 01	30 06	03	24	21	838	733	6 87	6 83	122	107	15
4 05	30 09	30 11	30 12	30 14	03	35	31	1,221	1,072	6 82	6 78	179	158	21
4 06	30 16	30 19	30 19	30 23	04	42	40	1,466	1,396	6 79	6 74	216	206	10
4 07	30 25	30 25	30 29	30 31	02	52	48	1,815	1,675	6 74	6 71	269	250	19
4 11	30 39	30 50	30 47	30 60	13	70	77	2,443	2,687	6 67	6 59	366	408	42
4 13	30 43	30 64	30 52	30 76	24	75	93	2 617	3,246	6 65	6 52	393	498	105
4 15½	30 47	30 81	30 58	30 96	38	81	1 13	2,827	3,944	6 63	6 44	426	612	186
4 17	30 48	30 90	30 61	31 07	46	84	1 23	2,932	4,293	6 63	6 39	442	672	230
4 19	30 48	31 02	30 62	31 21	58	85	1 38	2,966	4,816	6 63	6 33	447	761	314
4 21	30 49	31 13	30 65	31 34	69	88	1 51	3,141	5,270	6 62	6 28	464	839	375
4 22¼	30 495	31 20	30 67	31 42	75	90	1 59	3,141	5,550	6 62	6 24	474	889	415
4 25	30 49	31 37	30 69	31 62	93	92	1 79	3 211	6,247	6 62	6 16	485	1,014	529
4 26¼	30 495	31 41	30 70	31 68	98	93	1 85	3,246	6,456	6 62	6 14	490	1,051	561
4 28	30 52	31 51	30 74	31 80	1 06	97	1 97	3,385	6,875	6 61	6 09	512	1,129	617
4 29	30 53	31 55	30 76	31 85	1 09	99	2 02	3,455	7,050	6 60	6 07	523	1,161	638
4 30	30 565	31 58	30 78	31 89	1 11	1 01	2 06	3,525	7,189	6 59	6 05	535	1,188	653
4 31	30 57	31 64	30 82	31 96	1 14	1 05	2 13	3,664	7,434	6 58	6 02	557	1,235	678
4 32	30 59	31 67	30 85	32 00	1 15	1 08	2 17	3,769	7,573	6 57	6 01	574	1,260	686
4 33	30 595	31 73	30 86	32 07	1 21	1 09	2 24	3,804	7,818	6 57	5 98	579	1,307	728
4 34	30 63	31 755	30 90	30 11	1 21	1 13	2 28	3,954	7,957	6 55	5 96	604	1,335	731
4 35	30 67	31 80	30 95	32 16	1 21	1 18	2 33	4,118	8,132	6 53	5 94	631	1,369	738
4 36	30 695	31 83	30 98	32 20	1 22	1 21	2 37	4,223	8,271	6 52	5 92	648	1,397	749
4 37½	30 75	31 90	31 05	32 29	1 24	1 28	2 46	4,467	8,585	6 49	5 89	688	1,458	770
4 39	30 82	31 95	31 13	32 36	1 23	1 36	3 53	4,746	8,830	6 46	5 86	735	1,507	772
4 40	30 87	31 99	31 19	32 41	1 22	1 42	2 58	4,956	9,004	6 43	5 84	771	1,542	771
4 41	30 905	32 035	31 24	32 46	1 22	1 47	2 63	5,130	9,178	6 41	5 82	800	1,577	777
4 42	30 94	32 05	31 28	32 49	1 21	1 51	2 66	5,270	9,283	6 40	5 81	823	1,598	775
4 50	30 87	31 97												

*For loss of heat to room and in accordance with the assumption that the left hand was as large as the right.
†The first five numbers in this column are excesses of R over L, the rest excesses of L over R

("blood-flow" in this case being merely a phrase which it might be convenient to use for the sake of uniformity), it will come out greater immediately after the interruption of the circulation than later on, and will diminish steadily Where the flow is partially interrupted the slope of temperature in the hand may be expected to be altered also but to a less extent than after total interruption The flow calculated in the usual way will then come out somewhat greater than it actually is, but by and by

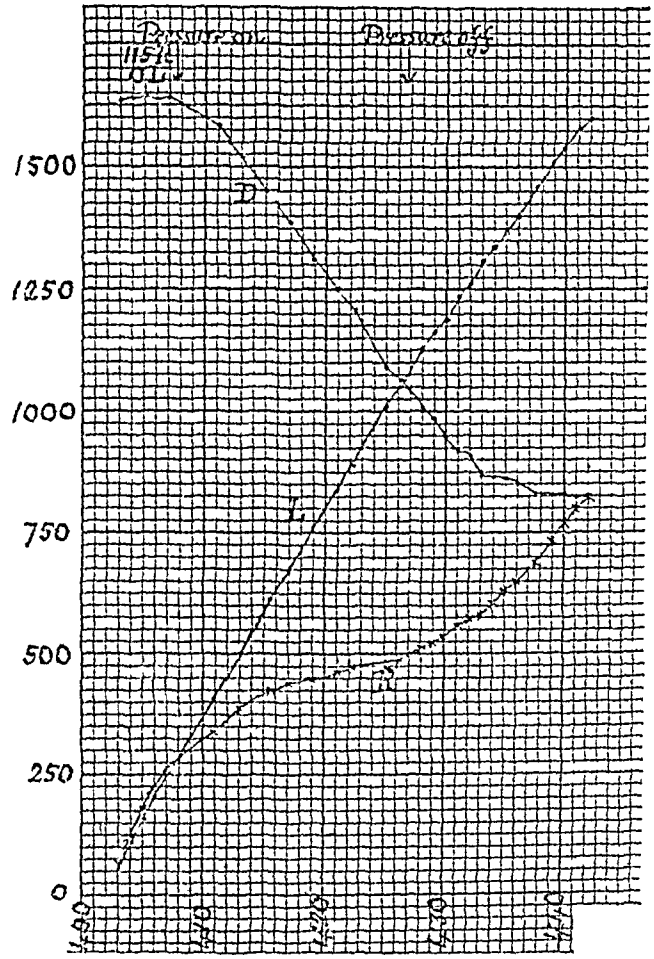

Fig 1 —R and L represent the change with the time measured from the beginning of the experiment in the quantity $\frac{H}{T-T'}$, which measures the blood flow, and D, the difference in this quantity for the two hands (Exper 1)

a steady slope of temperature will be again established and henceforth the calculated and the actual flows will be identical When the circulation is reestablished through the hand in which it has been completely stopped, some of the heat brought to the hand by the blood will at first go to heat the interior of the hand till the steady state has again been reached, and the calculated flow at first will therefore be less than the real flow Usually in the following pages the heat exchange has alone been given

when the circulation was totally or partially interrupted, and has not been translated into "blood-flow" Experiment 1 will illustrate the course of the heat exchange with total interruption of the circulation The results of this experiment, as displayed in Table 1, are plotted in two different ways in Figures 1 and 2

Experiment 1—M C, a healthy man, 23 years old 3 45 p m, systolic arterial pressure in right arm taken with Riva-Rocci apparatus (armlet 12 5 cm broad), 115 mm, in two observations (subject sitting) 3 49 p m Hands put into bath, armlet being left on right arm but disconnected from manometer Mouth temperature 36 75 C, pulse 88 (sitting), room 25 1 C 4 00 p m Calorimeter R 29 675 C, L 29 74 C, 3,015 c c water in each calorimeter 4 01 p m Hands put into calorimeters, right, as always, into R, left into L Armlet on right arm at once connected with manometer but no pressure made as yet At 4 07½ made pressure of 115 mm mercury on right arm At 4 26¾ released pressure At 4 37 p m removed armlet At 4 42 removed hands from calorimeter At end of experiment the right hand felt a little swollen Its volume was 493 c c, that of left 459 c c

In Figure 1 the quantity $\frac{H}{T - T'}$ (where T is the temperature of the arterial blood, T′ the mean temperature of the calorimeter, and H the heat given off to the calorimeter), reckoning from the first observation after the hands were introduced into the calorimeters, is plotted for each hand along the vertical and the time along the horizontal axis Thus, R and L in Figure 1 represent the way in which the quantity $\frac{H}{T - T'}$ increases with the time for right and left hand respectively When the flow is unhindered this quantity, multiplied by the reciprocal of the specific heat of blood, corresponds to the amount of blood which has passed through the hand from the beginning of the observations to the time represented by any point on the curve $\frac{H}{T - T'}$ is the quantity which measures the blood-flow on the assumption that the slope of temperature throughout the hand remains steady As already pointed out, this assumption is only justified for a hand through which the blood is steadily flowing and not for a hand in which the flow has suffered an abrupt change or been interrupted altogether Since in accordance with the plan of the experiments, interference with the circulation was always caused in at least one hand, it was considered that for most purposes it would be more instructive to compare the amounts of heat given off by the hands without reference to the factor T — T′ For this comparison it is enough to take the calorimeter temperatures at each time, corrected for loss of heat to the room and for the difference in the volume of the hands, and in all of the following Figures, including Figure 2, this has alone been done With unobstructed circulation, equal increments of temperature (thus corrected) correspond to equal blood-flows in the two hands so long as

the mean temperatures of the two calorimeters remain the same When the temperature of one calorimeter rises above that of the other the blood-flow through the hand whose calorimeter shows excess of temperature increases more rapidly than the excess of temperature For most of the experiments, however, the temperature of the calorimeters remained so nearly the same that when the curves representing the increase of temperature of the calorimeters (with unobstructed flow) are parallel to each other no serious error is introduced by assuming that the blood-flow in the two hands is then the same Still, to see whether with such changes of temperature as occurred in the calorimeter in any one experiment there would be any marked difference between the curves when plotted in the two

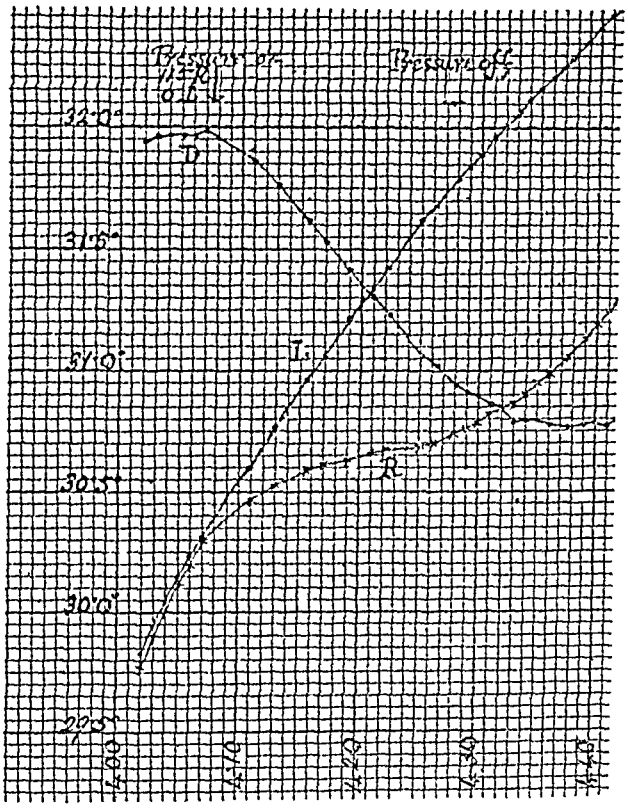

Fig 2.—R and L (corrected) calorimeter temperatures for right and left hand, respectively (in Experiment 1) D, differences in these temperatures R had not become quite horizontal when the pressure was released i e, the right hand was still giving off some heat to its calorimeter (not, however, due to a flow of blood in it, as shown in other experiments)

ways, both methods were adopted for Experiment 1, where the difference of temperature was greater than in any of the other experiments and where accordingly the difference between the curves yielded by the two methods would be at a maximum Inspection of Figures 1 and 2 shows that the results are not obscured whichever graphic method is adopted

Table 2 of the same experiment shows the quantities of heat given off by the two hands per 100 c c of hand per minute for seven periods.

making in the aggregate a little over thirty-four minutes The first period (five minutes) was before pressure had been raised in the armlet, and the last three periods after the pressure had been released

For a period of four and one-half minutes beginning two to three minutes after establishment in the cuff on the right arm of a pressure equal to the systolic pressure, the heat given off by the right hand was only 18 9 small calories per 100 c c per minute as compared with 73 6 calories before the pressure was established For the next five and one-half minutes the heat given off by the right hand was 8 9, for the next five and one-quarter minutes, pressure being still maintained on the right arm, only 6 7 small calories per 100 c c per minute If we take the heat production of the resting hand at 1 small calorie per 100 c c per minute,[1] this would leave, on the assumption that a steady slope of temperature had been again at this time established in the right hand, 5 7 small calo-

TABLE 2 (EXPERIMENT 1) —HEAT GIVEN OFF PER 100 C C OF HAND PER MINUTE

Period in Mins	Heat Given Off in Small Cal *		Mean Temp of Calorim's		Blood-Flow in Grams		Pressure in Armlet	
	R	L	R	L	R	L	R	L
5	73 6	70 9	30 01	30 04	12 14	11 74	0	0
4½	18 9	59 5	30 43	30 66		10 84	115	0
5½	9 0	74 7	30 48	30 97		13 11	115	0
5¼	6 7	47 4	30 49	31 27		9 91	115	0
4	18 6	37 7	30 56	31 59		8 11	0	0
4	24 8	37 7	30 64	31 75		8 38	0	0
6	35 4	35 2	30 82	31 94		8 13	0†	0

*Per 100 c c of hand per minute †Armlet off

lies per 100 c c per minute as the heat given off by the blood passing through the hand, corresponding to a flow of almost exactly 1 gm per 100 c c per minute or one-twelth of the original amount It is quite certain, however, that at the moment when the pressure in the cuff was released the steady state had not yet been attained in the hand and therefore the conclusion may safely be drawn, even from this experiment, which was not carried on for a sufficiently long time to afford a decisive test, that the flow, if any, in the right hand must have been less than one-twelfth of the unhindered flow

As already pointed out, on reestablishing the circulation a portion of the heat brought by the blood must go to warm the hand itself until a steady slope of temperature has been once more established The heat given off by the hand whose circulation was stopped must therefore for a

[1] Heart 1911, iii, 44

time be less than that given off by the other This is clearly shown in Experiment 1, Table 2 For the first four minutes after release of the pressure the right hand gave off only 18 6 calories per 100 c c per minute, about half the amount lost by the left hand Even ten minutes later it is probable that the steady state had not been attained since the flow

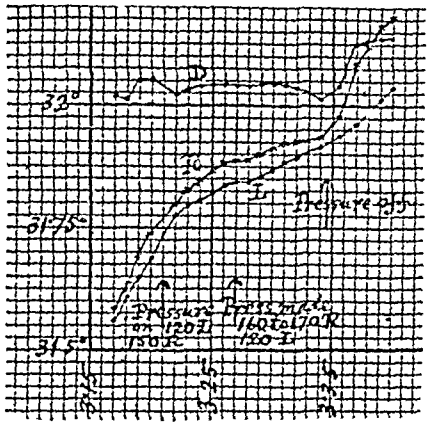

Fig 3 —R and L (corrected) calorimeter temperatures for right and left hands in Experiment 2, and D differences in these temperatures

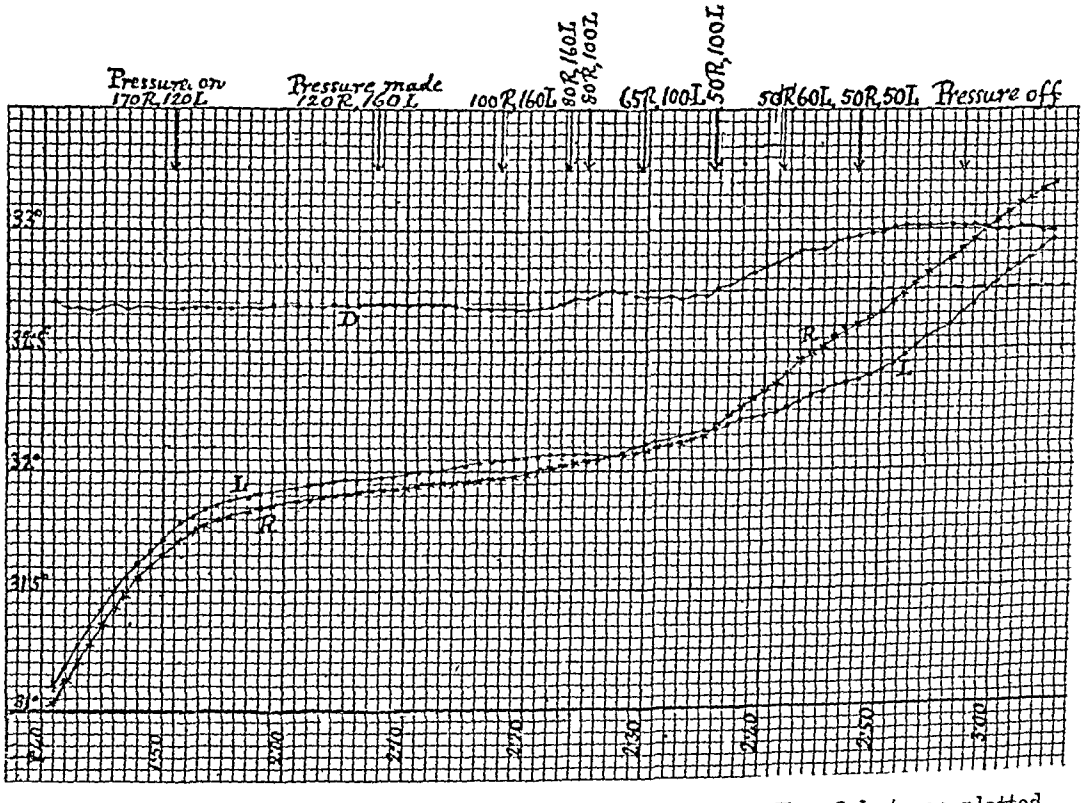

Fig 4 —R, L and D have the same signification as in Fig 3 but are plotted from Experiment 3, made with another person So long as the pressures are equal to or greater than systolic pressure, D is horizontal and R and L parallel

reckoned on the assumption that it had been reached, was only 6 63 gm for the right hand against 8 13 gm for the left It must be remembered

that the flow is directly proportional to the heat given off and inversely proportional to the difference between the mean temperature of the calorimeter and the temperature of the arterial blood coming to the hand

It was soon seen that it would be too tedious for the subject to continue the experiment in this form for a long enough time to insure that the loss of heat from the occluded hand had become steady Accordingly another method was adopted which did not require that the observation should be carried to this point This method had the further advantage that no assumption as to the amount of heat produced in the hand in the absence of a circulation needed to be made The systolic pressure was first determined in the two arms Then after a period during which the unobstructed blood-flow was measured in the two hands, a pressure equal to the systolic pressure was established in one armlet and simultaneously a pressure considerably higher than the systolic pressure, and therefore a pressure certainly enough to obliterate completely the arteries was made in the other Comparison of the heat given off by the two hands would now show whether there was any excess in the case of the first hand If not, it is clear that no blood could be passing through that hand Experiments 2 and 3 are examples on two different healthy persons The results of these experiments are graphically represented in Figures 3 and 4, respectively In these figures the temperatures of the two calorimeters (corrected for loss of heat and for the difference in the size of the two hands), and the differences at each minute between the two temperatures, as shown in Tables 3 and 4, are plotted along the vertical, and the time along the horizontal axis It will be observed that with systolic pressure on one arm and a very decidedly greater pressure on the other the curves of heat loss for the two hands remain practically parallel This could not be the case unless the circulation was completely stopped at the lower of the two pressures It is only when the pressure on one arm is diminished distinctly below the systolic pressure (Fig 4) that the curves begin to diverge

In Table 5 of Experiment 3, wherein the average heat exchange of the hands is calculated for four-minute to ten-minute periods throughout the experiment, the same result is brought out in another way For example the difference between the heat loss of the right and left hands remains practically unchanged by the application of pressures of 120 and 170 respectively to the right and left arms This could not be if the flow was completely stopped in one hand and not in the other The difference increases very markedly when the pressure is made 50 on the right and 100 on the left arm

Experiment 2.—Armlets were placed on both arms of M C Systolic pressure in right arm 120 mm and 118 mm in two observations with Riva-Rocci apparatus The subject was sitting in a high chair with his hands hanging down exactly in the position they would occupy in the calorimeters It was always in this position

TABLE 3 (EXPERIMENT 2).—EFFECT OF DIFFERENT PRESSURES ON HEAT GIVEN OFF BY HANDS AS SHOWN BY CALORIMETER TEMPERATURES

Time	Calorimeter Temperature					Time	Calorimeter Temperature				
	Actual		Corrected				Actual		Corrected		
	R	L	R	L	Diff		R	L	R	L	Diff
3 17	31 58	31 56			0 02	3 29	31 785	31 745	31 90	31 85	0 05
3 18	31 61	31 60	31 62	31 61	0 01	3 30	31 79	31 75	31 91	31 87	0 04
3 19	31 68	31 63	31 70	31 65	0 05	3 31	31 79	31 755	31 92	31 88	0 04
3 20	31 71	31 66	31 74	31 69	0 05	3 32	31 785	31 76	31 93	31 89	0 04
3 22	31 75	31 73	31 80	31 78	0 02	3 34	31 77	31 765	31 93	31 92	0 01
3 23	31 77	31 74	31 83	31 79	0 04	3 35½	31 80	31 77	31 98	31 94	0 04
3 24	31 78	31 76	31 85	31 80	0 05	3 37	31 895	31 78	32 09	31 96	0 13
3 25	31 79	31 75	31 87	31 82	0 05	3 38	31 92	31 80	32 12	31 99	0 13
3 26	31 795	31 755	31 88	31 84	0 04	3 39	31 95	31 82	32 16	32 02	0 14
3 27	31 79	31 755	31 89	31 85	0 04	3 40	31 96	31 83	32 18	32 04	0 14
3 28	31 78	31 745	31 88	31 84	0 04	3 52½	31 84	31 72			

TABLE 4 (EXPERIMENT 3) —CHANGES IN HEAT GIVEN OFF BY HANDS UNDER VARYING PRESSURES AS SHOWN BY CALORIMETER TEMPERATURES

Time	Calorimeter Temperature					Time	Calorimeter Temperature				
	Actual		Corrected				Actual		Corrected		
	R	L	R	L	Diff		R	L	R	L	Diff
1 40	31 02	31 09				2 24	31 51	31 57	32 03	32 06	0 03
1 41	31 03	31 11	31 04	31 12	0 08	2 25	31 505	31 56	32 04	32 07	0 03
1 42	31 09	31 16	31 11	31 18	0 07	2 26	31 505	31 54	32 05	32 06	0 01
1 43	31 17	31 24	31 21	31 28	0 07	2 27	31 50	31 54	32 06	32 06	0 00
1 44	31 23	31 31	31 28	31 36	0 08	2 28	31 50	31 55	32 07	32 08	0 01
1 45	31 30	31 37	31 36	31 43	0 07	2 29	31 50	31 555	32 08	32 10	0 02
1 46	31 37	31 43	31 44	31 50	0 06	2 30	31 50	31 56	32 09	32 11	0 02
1 47	31 395	31 47	31 48	31 55	0 07	2 31	31 495	31 56	32 10	32 12	0 02
1 48	31 465	31 53	31 56	31 62	0 06	2 32	31 50	31 56	32 12	32 14	0 02
1 49	31 495	31 56	31 60	31 66	0 06	2 33	31 495	31 565	32 13	32 16	0 03
1 50	31 535	31 61	31 65	31 72	0 07	2 34	31 50	31 555	32 14	32 15	0 01
1 51½	31 58	31 66	31 72	31 79	0 07	2 35	31 50	31 555	32 15	32 16	0 01
1 52½	31 60	31 67	31 75	31 81	0 06	2 36	31 52	31 555	31 19	32 18	0 01*
1 53½	31 62	31 69	31 78	31 84	0 06	2 37	31 55	31 56	32 23	32 20	0 03
1 54½	31 625	31 70	31 80	31 87	0 07	2 38	31 575	31 565	32 26	32 21	0 05
1 55½	31 63	31 705	31 81	31 88	0 07	2 39	31 595	31 56	32 30	32 22	0 08
1 57	31 63	31 70	31 83	31 89	0 06	2 40	31 62	31 57	32 33	32 24	0 09
1 58	31 635	31 71	31 85	31 91	0 06	2 41	31 63	31 565	32 36	32 25	0 11
1 59	31 635	31 705	31 86	31 92	0 06	2 42	31 67	31 57	32 41	32 26	0 15
2 01	31 63	31 70	31 88	31 94	0 06	2 43	31 71	31 59	32 46	32 29	0 17
2 02	31 62	31 69	31 88	31 94	0 06	2 44	31 72	31 60	32 48	32 31	0 17
2 03	31 615	31 69	31 89	31 95	0 06	2 45	31 735	31 605	32 51	32 33	0 18
2 04	31 615	31 685	31 90	31 96	0 06	2 46	31 77	31 615	32 55	32 35	0 20
2 05	31 61	31 685	31 91	31 97	0 06	2 47	31 78	31 61	32 58	32 36	0 22
2 06	31 605	31 675	31 91	31 97	0 06	2 48	31 80	31 62	32 61	32 38	0 23
2 07	31 605	31 67	31 93	31 98	0 05	2 49	31 815	31 625	32 64	32 40	0 24
2 08	31 595	31 66	31 93	31 98	0 05	2 50	31 82	31 63	32 65	32 41	0 24
2 09	31 58	31 65	31 93	31 98	0 05	2 51	31 855	31 65	32 70	32 44	0 26
2 10	31 58	31 65	31 94	31 99	0 05	2 52	31 88	31 67	32 74	32 47	0 27
2 11	31 575	31 645	31 94	31 99	0 05	2 53	31 91	31 70	32 78	32 51	0 27
2 12	31 57	31 64	31 95	32 00	0 05	2 54	31 935	31 73	32 82	32 56	0 26
2 13	31 565	31 635	31 96	32 01	0 05	2 56	31 98	31 76	32 87	32 60	0 27
2 14	31 55	31 63	31 96	32 02	0 06	2 57	32 01	31 805	32 91	32 65	0 26
2 15	31 54	31 63	31 96	32 03	0 07	3 58	32 04	31 83	32 96	32 69	0 27
2 16	31 535	31 625	31 96	32 03	0 07	2 59	32 08	31 875	33 01	32 75	0 26
2 17	31 53	31 62	31 97	32 04	0 07	3 00	32 10	31 90	33 03	32 78	0 25
2 18	31 525	31 615	31 98	32 05	0 07	3 01	32 13	31 93	33 07	32 82	0 25
2 19	31 515	31 61	31 98	32 05	0 07	3 02	32 15	31 94	33 10	32 84	0 26
2 20	31 515	31 605	31 99	32 06	0 07	3 03	32 16	31 95	33 13	32 87	0 26
2 21	31 515	31 60	32 00	32 06	0 06	3 04	32 18	31 99	33 16	32 92	0 24
2 22	31 51	31 595	32 01	32 07	0 06	3 05	32 20	32 01	33 19	32 95	0 24
2 23	31 51	31 585	32 02	32 07	0 05	3 29	31 915	31 74			

*From this to the end of the table the differences represent excesses of temperature of R over L, before the excesses of temperature of L over R

that the pressures were determined in this series of experiments Disconnected armlets from manometers and put hands in bath at 2 45 p m , mouth temperature 36 75 rectal 37 225, pulse 87, room temperature 24 0 At 2 56¼ p m hands put into calorimeters, as always, 3 015 c c water in each Between 3 20¼ and 3 21 p m a pressure of 120 mm mercury was established in left armlet and 150 mm in right At 3 27 p m increased pressure in right to 160 to 170 At 3 34½ p m pressure released in both cuffs At 3 40 p m hands taken out of calorimeters Volume of right hand 465 c c , of left 465 c c

Experiment 3—C B , normal man, aged 23 years Systolic pressure (with Riva-Rocci apparatus) right arm 114 and 113 in two observations, left arm 116, 118 and 116 in three observations Subject sitting with hands in position they occupy when in calorimeters Hands put in bath at 1 30 p m , after disconnecting manometers Mouth temperature 36 75 C rectal 37 2 C , pulse 104 Room temperature 23 8 C to 24 3 C throughout experiment At 1 40⅓ p m hands put into calorimeters, 3,015 c c water in each Between 1 50½ and 150 5/6

TABLE 5 (EXPERIMENT 3) —QUANTITY OF HEAT GIVEN OFF BY HANDS UNDER VARYING PRESSURES

Period in Minutes	Heat Given Off (Small) Cal per 100 c c Hand per Min			Mean Temp of Calorim's		Pressure on Arm	
	R	L	Diff	R	L	R	L
9	57 04	56 51	0 53	31 28	31 32	0	0
4	20 42	19 63	0 79	31 61	31 68	170	120
5½	9 89	8 48	1 41	31 63	31 71	170	120
6	6 28	5 37	0 91	31 62	31 69	170	120
9	3 91	5 62	1 71*	31 57	31 64	120	160
5	7 53	4 42	3 11	31 52	31 60	100	160
10	9 53	9 08	0 45	31 50	31 56	80	100
5	28 54	11 16	17 38	31 58	31 56	50	100
5	28 54	16 30	12 24	31 73	31 59	50	60
9	29 53	26 94	2 59	31 91	31 71	50	50
8	29 85	31 26	1 41	32 11	31 91	0	0

*Excess of left over right The other numbers in this column are excesses of right over left

p m a pressure of 120 mm mercury was established in the left armlet and 170 mm in right These pressures were maintained (within 2 mm) till 2 07½ p m when the pressure in the left armlet was made 160 mm and that in the right 120 mm No change till 2 17¾ p m , when the pressure in the right was lowered to 100 mm , that in left remaining 160 mm It was soon noticed that the right forearm became red The contrast in color between it and the left became striking At 2 23⅓ p m lowered pressure in right to 80 mm , and at 2 24 5/6 p m lowered pressure in left to 100 mm At 2 29½ p m made pressure in right 65 mm keeping left at 100 mm At 2 35½ p m pressure in right reduced to 50 mm At 2 41½ p m pressure in left reduced to 60 mm , keeping right at 50 mm At 2 47 5/6 p m pressure was also made 50 mm in left At 2 57 pressure released completely in both armlets At 3 05 p m hands removed from calorimeters Systolic pressure again measured Right brachial 116 and 117 in two observations, left 112, 114, 116 in three observations Volume of right hand 445 c c , of left 442 c c As both hands felt swollen, the volume was again measured at 5 00 p m and found to be 410 c c for right, and 405 c c for left

TABLE 6 (EXPERIMENT 4) —CALORIMETER TEMPERATURES WITH PRESSURES BELOW SYSTOLIC PRESSURE

Time	Calorimeter Temperature					Time	Calorimeter Temperature				
	Actual		Corrected				Actual		Corrected		
	R	L	R	L	Diff		R	L	R	L	Diff
3 35	29 67	29 655			0 015	3 50	30 05	30 43	30 23	30 64	0 41
3 36	29 73	29 73	29 742	29 744	0 002	3 51½	30 06	30 48	30 258	30 711	0 453
3 37	29 81	29 82	29 834	29 848	0 014	3 53	30 08	30 53	30 296	30 782	0 486
3 38	29 89	29 88	29 926	29 922	0 004*	3 54	30 095	30 55	30 323	30 816	0 493
3 42½	30 02	30 04	30 11	30 145	0 035	3 55	30 11	30 62	30 35	30 90	0 55
3 44	30 03	30 11	30 138	30 236	0 098	3 57	30 16	30 69	30 424	30 998	0 574
3 45½	30 035	30 17	30 161	30 317	0 156	3 58	30 185	30 725	30 461	31 047	0 586
3 47	30 05	30 28	30 194	30 448	0 254	3 59	30 21	30 74	30 498	31 08	0 582
3 48½	30 05	30 36	30 212	30 549	0 337	4 00	30 25	30 80	30 55	31 15	0 60
						4 12	30 11	30 64			

* Excess of R over L The other numbers in this column are excesses of L over R

SECTION II THE INFLUENCE ON THE FLOW IN THE HANDS OF PRESSURES IN THE ARMLETS LESS THAN THE SYSTOLIC PRESSURE

If the blood-flow is completely arrested at a pressure equal to the systolic pressure, it is a question of some interest how it increases as the pressure in the cuff is lowered from the systolic pressure, or, what probably comes to the same thing, how the flow diminishes as the pressure in the cuff is raised from zero toward the systolic pressure

In Experiment 4 the heat given off by the right hand was compared with that given off by the left when a pressure somewhat below the systolic pressure was maintained on the right arm while the flow through the left arm and hand was unobstructed The results are graphically shown in Figure 5, constructed from Table 6

TABLE 7 (EXPERIMENT 4) —HEAT GIVEN OFF UNDER PRESSURES BELOW SYSTOLIC PRESSURE

Period in Mins	Heat Given Off in Small Cals *		Mean Temp of Calorimeters		Blood-Flow in gm *		Pressure in Armlet	
	R	L	R	L	R	L	R	L
3	63 4	69 9	29 78	29 77	10 46	11 53	0	0
4½	13 3	52 8	30 04	30 16		9 25	90	0
3	8 7	50 1	30 05	30,36		9 07	90	0
3½	19 1	41 9	30 09	30 55		7 8	0	0
5	29 8	39 6	30 18	30 71		6 8	0	0

*Per 100 c c of hand per minute

Experiment 4—M C, Armlet of Erlanger sphygmomanometer adjusted on right arm but not yet connected with manometer At 3 22 p m hands put into both at 3 33½ p m hands put into calorimeters and armlet on right arm connected with manometer, but no pressure yet produced Between 3 39 and 3 39½ p m made pressure of 90 mm mercury on right arm and maintained it until 3 50½ p m when pressure was released Hands removed from calorimeters at 4 00 p m Systolic pressure in right arm 100 to 105 mm in seven separate observations Volume of right hand 465 c c, of left 435 c c, pulse 76 (sitting), mouth temperature 36 5 C, 3,015 c c water in each calorimeter

If we compare Experiments 1 and 4 done on the same man on successive days, it is seen that with a pressure of from 10 to 15 mm below the systolic pressure the heat given off was reduced nearly as much as with a pressure equal to the systolic pressure In other words, a pressure in the cuff 10 or 15 mm below the systolic pressure constituted an almost impervious block Thus in Table 7, Experiment 4, for the first period of four and one-half minutes after the establishment of the pressure the heat

given off by the right hand fell from 63 4 small calories per 100 c c of hand per minute, before the pressure was raised, to 13.3, and then, in the second period of three minutes, to 8 7, or less than one-seventh of the initial amount As already remarked, the decrease in the blood-flow must be still greater. This experiment was done by the first method, and as previously explained, it could not be satisfactorily continued for a time long enough to eliminate entirely the effect due to change in the slope of temperature in the hand after the circulation was interfered with In all the other experiments cited in this section of the paper the effect of a pressure below the systolic pressure on the heat given off by one hand was compared with the effect of a pressure equal to, or greater than, the systolic pressure on the other hand Thus, in Experiment 5 with a mean systolic pressure of 113 mm in the right brachial and 118 in the left, the heat given off by the two hands was compared when the pressure in the left

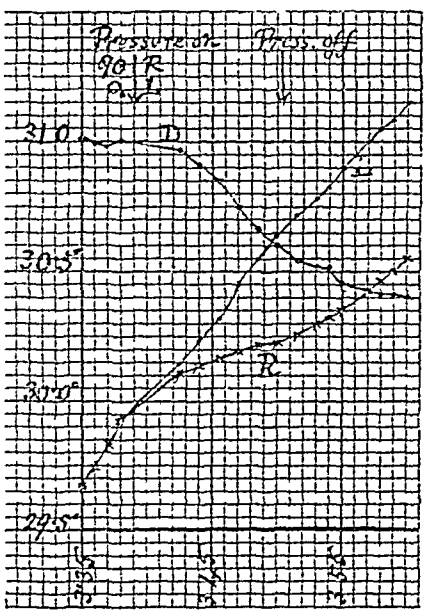

Fig 5—R and L (corrected) calorimeter temperature of right and left hand respectively, D differences between those temperatures The curves are plotted from Experiment 4

armlet was made 120 (enough to stop the flow completely) and in the right 65 mm In the first ten minutes after the establishment of the pressure the heat given off by the left hand was reduced to between one-sixth and one-seventh of the initial amount, while that given off by the right was reduced only to a little less than one-half The blood-flow in the right hand (on the assumption that the initial slope of temperature in the right hand remains undisturbed i e without allowing for any cooling of the hand, which would, of course, in any case be much less than for the hand in which the circulation was completely interrupted) works out at 7 45 gm per 100 c c of hand per minute for the ten-minute period as compared with 14 07 gm before pressure was made So that the handicap

of 65 mm pressure in the armlet did not cut down the circulation quite to half Probably the reduction was even considerably less than this For on releasing the pressure, the flow, at least during the eight minutes for which it was still observed, did not regain its original volume, averaging only 9 38 gm per 100 c c per minute for the right hand Although a portion of this decline in flow is only apparent, and due to reheating of the hand, the fact that the flow in the left hand almost recovered its original ratio to that in the right within the eight-minute period indicates that the flow was in any case diminishing throughout the latter part of the experiment, and a portion of the diminution produced in the heat exchange of the right hand during the pressure period may be attributed to this cause

Experiment 5—M C Hands put in bath at 2 08 p m Put armlets on (Riva-Rocci on right, Erlanger on left) and measured systolic pressure with hands in bath Right arm 112, 114 mm in two observations, left arm 116, 120, mouth temperature 36 8 C Hands put into calorimeters at 2 27½ p m 3,015 c c water

TABLE 8—HEAT GIVEN OFF DURING EXPERIMENT 5

Period in Mins	Heat Given Off in Small Cals *		Mean Temp of Calorimeters		Blood-Flow in gm *		Pressure in Armlet	
	R	L	R	L	R	L	R	L
8	76 09	74 21	30 79	30 83	14 7	13 81	0	0
10	35 52	11 64	31 50	31 35			65	120
8	41 2	42 2	31 91	31 57	9 38	8 99	0	0

*Per 100 c c of hand per minute

in each At 2 37½ p m got up pressure of 65 mm mercury in right and 120 mm in left, and maintained these pressures till 2 50½ p m, when they were released At 2 59 p m removed hand from calorimeters, dried and again measured systolic pressure in right arm (112 mm) Volume of right hand 480 c c, of left 461 c c Room 24 2 C

Experiment 6—C B Riva Rocci on right arm, Erlanger on left Systolic pressure, right arm 110, 106, 100 (average 105), left arm 104, 96, 98 (average 100) At 3 19 p m hands put into bath, at 3 30 into calorimeters, 3,015 c c water in each Pulse 106 (sitting), mouth temperature 36 5 C rectal 37 0 C Between 3 40½ and 3 40¾ p m pressure raised in armlets to 90 mm mercury in right, 100 mm in left At 3 48 made pressure 80 mm in right, 110 in left At 3 53 p m made pressure 80 mm in right, 120 in left At 3 57 made pressure in left 130, keeping right at 80 At 4 03 p m raised pressure in right to 130, keeping left at 130 At 4 10 p m released pressure in both armlets At 4 18 removed hands from calorimeters, dried them and again measured systolic pressure with hands in the same position as during the experiment, right 106, 107, left 108, 112, 104, 108 (average 108) Volume of right hand 430 c c, left 424 c c

In Experiment 6, from the data of which Figure 6 has been constructed, it is seen that when a pressure equal to the average systolic

TABLE 9.—CALORIMETER TEMPERATURES DURING EXPERIMENT 6

Time	Calorimeter Temperature					Time	Calorimeter Temperature				
	Actual		Corrected				Actual		Corrected		
	R	L	R	L	Diff		R	L	R	L	Diff
3 31½	29 85	29 93			0 08	3 56½	30 68	30 82	30 905	31 02	0 115
3 32½	29 94	30 03	29 949	30 038	0 089	3 57½	30 69	30 815	30 924	31 023	0 099
3 33½	30 01	30 11	30 028	30 126	0 098	3 58½	30 71	30 81	30 953	31 026	0 073
3 34½	30 09	30 20	30 117	30 224	0 107	3 59½	30 71	30 81	30 962	31 034	0 072
3 35½	30 75	30 31	30 211	30 342	0 131	4 00½	30 72	30 81	30 981	31 042	0 061
3 36	30 21	30 35	30 25	30 386	0 136	4 01½	30 735	30 805	31 005	31 045	0 040
3 37	30 29	30 44	30 339	30 484	0 145	4 02½	30 75	30 805	31 029	31 053	0 024
3 38	30 35	30 53	30 408	30 582	0 174	4 03½	30 755	30 805	31 043	31 061	0 018
3 39	30 41	30 61	30 477	30 67	0 193	4 04½	30 77	30 80	31 067	31 064	0 003*
3 40	30 45	30 65	30 526	30 718	0 192	4 05½	30 78	30 805	31 086	31 077	0 009*
3 41½	30 50	30 72	30 59	30 80	0 210	4 06½	30 785	30 80	31 100	31 08	0 020*
3 42½	30 53	30 73	30 629	30 818	0 189	4 07½	30 79	30 79	31 114	31 078	0 036*
3 43½	30 55	30 76	30 658	30 856	0 198	4 08½	30 785	30 79	31 118	31 086	0 032*
3 44½	30 57	30 78	30 687	30 884	0 197	4 09½	30 78	30 79	31 122	31 094	0 028*
3 45½	30 57	30 79	30 696	30 902	0 206	4 10½	30 79	30 79	31 141	31 102	0 039*
3 46½	30 58	30 79	30 715	30 91	0 195	4 11½	30 81	30 83	31 170	31 150	0 020*
3 47½	30 575	30 79	30 719	30 918	0 199	4 12½	30 825	30 86	31 194	31 188	0 006*
3 48½	30 59	30 81	30 743	30 946	0 203	4 14	30 84	30 92	31 222	31 260	0 038
3 49½	30 59	30 80	30 752	30 944	0 192	4 15	30 84	30 92	31 231	31 268	0 037
3 50½	30 595	30 81	30 766	30 962	0 196	4 16	30 85	30 93	31 25	31 282	0 032
3 51½	30 60	30 81	30 78	30 97	0 190	4 17	30 865	30 95	31 274	31 31	0 036
3 52½	30 61	30 81	30 799	30 978	0 179	4 18	30 88	30 955	31 298	31 323	0 025
3 53½	30 62	30 82	30 818	30 996	0 178	4 35	30 72	30 815			
3 54½	30 63	30 82	30 837	31 004	0 167						
3 55½	30 65	30 82	30 866	31 012	0 146						

*Excess of R over L All the other numbers in this column are excesses of L over R

pressure was established in the left armlet and a pressure (90 mm) 15 mm below average systolic pressure in the right armlet, the curves of heat loss remained practically parallel for the two hands With 80 mm in the right armlet an increase in the heat given off by the right hand, distinct though not great, is shown With a handicap of 80 mm mercury, say 25 mm below the systolic pressure, in the right armlet a sensible although still only a relatively small amount of blood was able to find its way below the cuff, whereas a pressure of 90 mm in the armlet formed almost a complete barrier

In Table 10, Experiment 6, it will be observed that with unobstructed circulation the left hand showed an excess of heat given off of 11 28 small

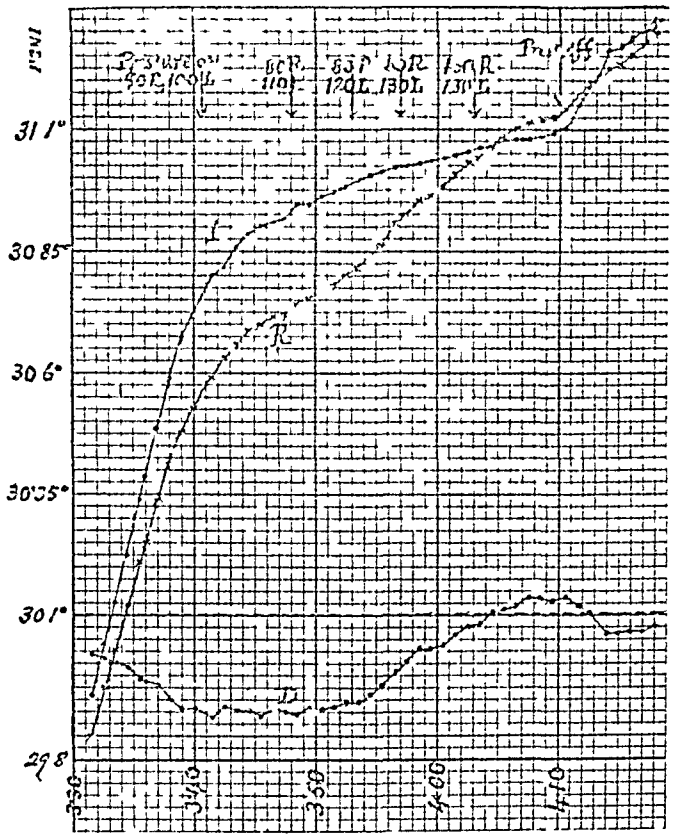

Fig 6—R, L and D the same as in the preceding figure but plotted from Experiment 6

calories per 100 c c per minute, as compared with the right The calculated blood-flow (not shown in the table) was 11 45 gm per 100 c c of hand per minute for the right, and 13 46 gm for the left, an excess of nearly 20 per cent for the left This, the opposite of the usual relation between the hands in right-handed persons, is doubtless due to some accidental temporary difference of vasomotor tone in the two hands The establishment of a pressure of 100 mm mercury on the left arm, and 90 mm on the right, completely wiped out the excess of heat loss from

the left hand, converting it into a slight excess for the right The difference between the two hands with these pressures in the armlets was so slight as to indicate that only a very small part of the heat loss by the right hand could have been due to the circulation of blood in it When the pressure in the right armlet was reduced to 80 mm the heat given off by the right hand at once increased, while that given off by the left still continued to fall owing to equalization of the temperature of the left hand and the calorimeter For the twelve minutes during which the handicap of the right arm was 80 mm , the average amount of heat given off by the right hand per 100 c c per minute was, in round numbers, 18 small calories and by the left 6 small calories The difference, 12 small calories per 100 c c per minute, represents the heat given off by blood flowing through the right hand, amounting to about 20 per cent of the initial unhindered flow

TABLE 10 —HEAT GIVEN OFF DURING EXPERIMENT 6

Period in Mins	Heat Given Off (Small Cals) per 100 c c Hand per Minute			Pressure in Armlet	
	R	L	Diff	R	L
8½	63 97	75 25	11 28*	0	0
6	17 32	16 19	1 13	90	100
4	14 01	6 66	7 35	80	110
3	23 95	6 76	17 19	80	120
5	17 58	4 86	12 72	80	130
4	7 56	3 65	3 91	130	130
7½	17 05	24 27	7 22*	0	0

*Excess of left over right The other numbers in this column are excesses of right over left

In the latter part of Experiment 3 (see Experiment 3 Table 5), it is seen that with a pressure of 50 mm in the armlet, when the systolic pressure was about 115, the handicap was only slight, the heat given off increasing only to a very small extent on releasing the pressure The change in the right hand, which had been longest subjected to the lower handicap, is taken as a more accurate gauge of the value of the handicap than that in the left, since the alteration of the slope of temperature in the hand following removal of the pressure would be less The increase on reducing the pressure on the right armlet from 80 to 50 mm was much greater than when it was reduced from 100 to 80 mm The flow for the first period of nine minutes, with unobstructed circulation, comes out 11 54 gm per 100 c c per minute for the right and 11 42 gm for the left, calculated on the volume of the hands after the swelling had subsided

For the first period of five minutes after the pressure on the right arm had been reduced to 50 mm., the flow for the right hand was 6.13 gm. and for the second period of five minutes, 6.31 gm. per 100 c.c. per minute. For the next nine minutes it was 6.78 gm., or about 59 per cent. of the initial flow. In reality the handicap caused by a pressure of 50 mm. does not reduce the flow nearly as much as 41 per cent. For the calculated flow for the eight minutes after the pressure was released is only 7.15 gm. per 100 c.c. per minute for the right, and 7.17 gm. for the left. This is only 5 per cent. more than the flow in the right hand with 50 mm. pressure in the armlet. The actual flow, no doubt, would be somewhat greater since a portion of the heat given up by the blood would go to heat the hand. Still, the unhindered flow at this period in the experiment was certainly far below the initial flow, as might be expected after such a prolonged immersion, and, therefore, the reduction caused by 50 mm. pressure in the armlet was almost certainly much nearer to 10 per cent. than to 40 per cent.

In the next series of experiments (Experiments 7, 8 and 9) a pressure equal to or greater than the systolic pressure was maintained in one cuff, while the pressure in the other originally raised to or above the systolic pressure, was allowed to fall slowly and continuously, the calorimeter temperatures being read from minute to minute. It was thought that by plotting curves showing for each minute the rate of loss of heat for each hand and the pressure in the cuff in which it was allowed to vary, any abrupt change in the blood-flow, as the pressure fell, would be easily detected. The curves reproduced in Figures 7 to 9 (constructed from Tables 11, 12 and 13, Experiments 7 to 9), show that this expectation was fulfilled.

Experiment 7.—C. B. Volume of right hand at beginning of experiment 400 c.c., of left 385 c.c. before armlets were put on. A Riva-Rocci armlet 12½ cm. wide was now put on each arm. Systolic pressure right arm 118 mm., left 114 mm. At 3 19½ p. m. hands put into bath after detaching manometers. Room temperature 23.3 C., mouth temperature 36.3 C., rectal 37.2 C., pulse 80 (sitting). At 3 31½ p. m. hands put into calorimeters, 3,015 c.c. water in each. Connected manometers with armlets without getting up any pressure. Between 3 39½ and 3 39¾ p. m. made pressure 120 mm. mercury in each cuff. Kept the pressure steady at 120 in left, allowing that in right to fall slowly. At 4 17 pressure released in both armlets. At 4 27 hands removed from calorimeters. Volume of right hand now 421 c.c., of left 418 c.c., with armlets still on but no pressure. Systolic and diastolic pressures were now determined by the Erlanger sphygmomanometer. Right arm, systolic 118, diastolic 78, systolic 118 and diastolic 78 in two observations. Left arm systolic 122, diastolic 78. At 5 03 p. m., after armlets were taken off, volume of right hand 402 c.c., of left 395 c.c.

Experiment 8.—M. C. Riva Rocci broad armlets on both arms. Systolic pressure right 122, 124, left 126, 124 in two observations. Volume of hands with armlets on but loose and with no pressure, right 477 c.c., left 455 c.c. Hands put into bath at 2 33½ p. m. Mouth temperature 36.8 C., rectal 37.5 C., room 21.4 C., pulse 100 (sitting). At 2 45½ p. m. hands put into calorimeters, 3,015 c.c. water in each. Between 2 54½ and 2 54¾ p. m. pressure raised to 130 mm. mercury in each armlet. Maintained this in left while allowing right to fall

TABLE 11.—RECORD OF CALORIMETER TEMPERATURES UNDER VARYING PRESSURES IN EXPERIMENT 7

Time	Calorimeter Temperature					Pressure in Right Armlet	Time	Calorimeter Temperature					Pressure in Right Armlet
	Actual		Corrected					Actual		Corrected			
	R	L	R	L	Diff			R	L	R	L	Diff	
3 33	30 35	30 29			0 06		3 58	30 575	30 525	30 847	30 777	0 070	57
3 34	30 39	30 33	30 401	30 341	0 06		3 59	30 58	30 52	30 863	30 783	0 080	56
3 35	30 41	30 36	30 432	30 381	0 051		4 00	30 585	30 515	30 879	30 788	0 091	55
3 36	30 44	30 40	30 473	30 432	0 041		4 02	30 595	30 505	30 911	30 794	0 097	54
3 37	30 485	30 46	30 529	30 502	0 027		4 04	30 60	30 495	30 938	30 800	0 138	53
3 38	30 50	30 48	30 555	30 533	0 022		4 06	30 61	30 48	30 970	30 801	0 169	51 5
3 39	30 515	30 51	30 580	30 573	0 007	0	4 08	30 625	30 465	31 006	30 801	0 205	50
3 40½	30 53	30 53	30 612	30 609	0 003	112	4 10	30 665	30 44	31 068	30 792	0 276	48
3 41½	30 535	30 535	30 628	30 624	0 004	106	4 11	30 675	30 435	31 089	30 797	0 292	47
3 42½	30 535	30 535	30 639	30 635	0 004	101	4 12	30 68	30 43	31 105	30 803	0 302	45
3 43½	30 54	30 535	30 654	30 645	0 009	97	4 13	30 69	30 43	31 126	30 813	0 313	44
3 44½	30 545	30 54	30 670	30 651	0 019	92 5	4 14	30 69	30 43	31 137	30 824	0 313	43
3 45½	30 55	30 545	30 686	30 666	0 020	88	4 15	30 69	30 425	31 148	30 829	0 319	42
3 46½	30 55	30 545	30 697	30 677	0 020	86	4 16	30 695	30 42	31 164	30 835	0 329	40
3 47½	30 55	30 545	30 708	30 687	0 021	81	4 17	30 695	30 415	31 175	30 840	0 335	0
3 48½	30 55	30 55	30 719	30 703	0 016	78	4 18	30 695	30 43	31 185	30 866	0 319	
3 49½	30 55	30 55	30 730	30 713	0 017	75	4 19	30 697	30 46	31 198	30 906	0 292	
3 50½	30 545	30 545	30 736	30 719	0 017	72	4 21	30 697	30 53	31 220	30 993	0 227	
3 51½	30 55	30 54	30 752	30 724	0 028	69	4 22	30 697	30 54	31 231	31 013	0 218	
3 52½	30 55	30 535	30 763	30 730	0 033	67	4 23	30 695	30 55	31 240	31 034	0 206	
3 54	30 555	30 53	30 784	30 740	0 044	63	4 24	30 69	40.56	31 246	31 054	0 192	
3 55	30 56	30 53	30 800	30 751	0 049	61	4 25	30 695	30 565	31 262	31 070	0 192	
3 56	30 565	30 53	30 816	30 761	0 055	59	4 26	30 69	30 58	31 268	31 095	0 173	
3 57	30 57	30 525	30 832	30 767	0 065	58	4 27	30 69	30 595	31 279	31 121	0 158	
							4 57	30 36	30 28				
							5 00	30 33	30 26				

slowly At 3 19½ p m pressure released in both At 3 29 p m hands taken out of calorimeters Volume of hands again measured (with armlets off), right 496 c c, left 490 c c Replaced armlets and measured systolic and diastolic pressures with Erlanger apparatus Right Systolic 122, diastolic 88, another observation, diastolic 90, another diastolic 86, another observation, systolic 120,

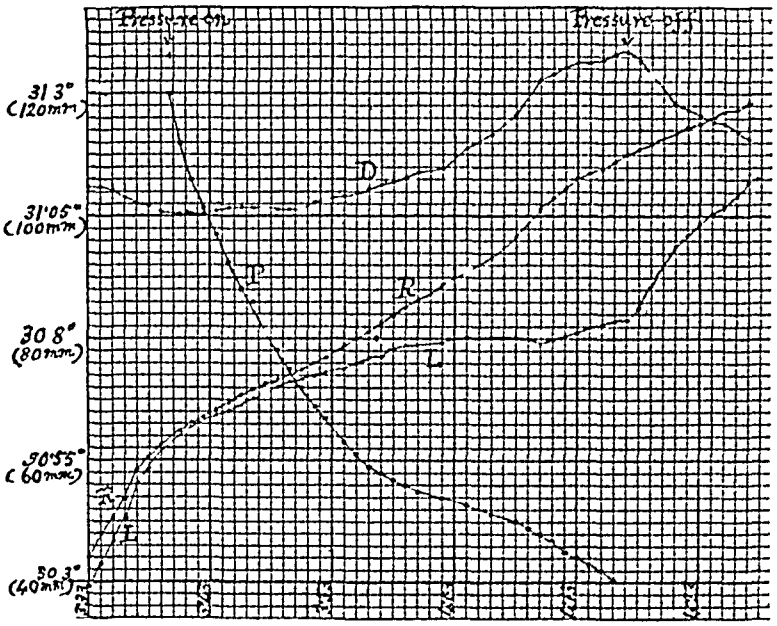

Fig 7—R and L (corrected) calorimeter temperatures for right and left hands, respectively, D, differences between these temperatures, P, curve showing fall of pressure in right armlet Plotted from Experiment 7

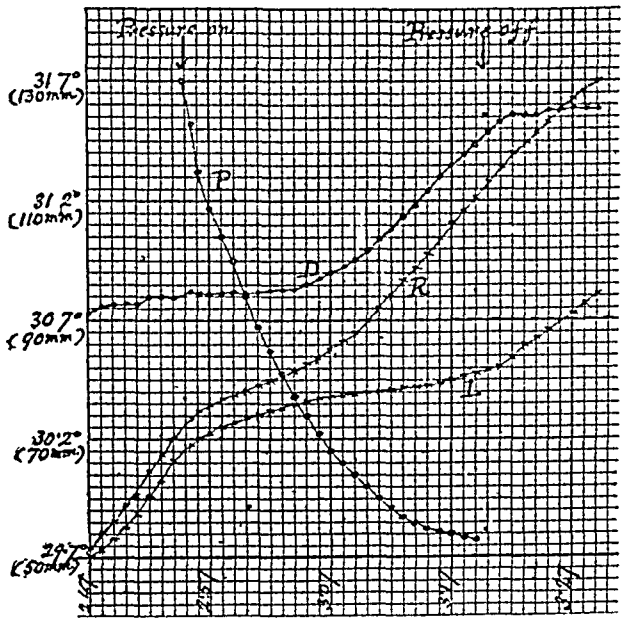

Fig 8—The letters have the same signification as in Fig 7, but the curves are plotted from Experiment 8

diastolic 88 Left arm Systolic 124, diastolic 94, another observation, systolic 128, diastolic 90 Repeated measurement on right arm diastolic 90, systolic 126, diastolic 82 As always, the hands were hanging down as if in the calorimeters, subject seated

TABLE 12.—RECORD OF CALORIMETER TEMPERATURES, EXPERIMENT 8

Time	Calorimeter Temperature					Pressure in right Armlet	Time	Calorimeter Temperature					Pressure in right Armlet
	Actual		Corrected					Actual		Corrected			
	R	L	R	L	Diff *			R	L	R	L	Diff	
2 47	29 74	29 705			0 035		3 09	30 315	30 085	30 645	30 393	0 252	64
2 48	29 79	29 73	29 805	29 744	0 061		3 10	30 35	30 08	30 695	30 402	0 293	62
2 49	29 825	29 755	29 855	29 783	0 072		3 11	30 395	30 07	30 755	30 406	0 349	60
2 50	29 87	29 795	29 915	29 837	0 078		3 12	30 425	30 065	30 80	30 415	0 385	58 5
2 51	29 90	29 84	29 96	29 896	0 064		3 13	30 475	30 06	30 865	30 424	0 441	57
2 52	29 98	29 89	30 065	29 960	0 105		3 14	30 51	30 05	30 915	30 428	0 487	56
2 53	30 05	29 95	30 14	30 034	0 106		3 15	30 565	30 045	30 985	30 437	0 548	55
2 54	30 10	30 01	30 205	30 108	0 097	0	3 16	30 61	30 035	31 045	30 441	0 604	54 5
2 55½	30 17	30 06	30 297	30 179	0 118	123	3 17	30 655	30 035	31 105	30 455	0 650	54
2 56	30 18	30 075	30 315	30 201	0 114	115	3 18	30 695	30 03	31 160	30 464	0 696	53 5
2 57	30 195	30 09	30 345	30 230	0 115	109	3 19	30 73	30 03	31 210	30 478	0 732	53
2 58	30 205	30 10	30 370	30 254	0 116	104	3 20	30 79	30 03	31 285	30 492	0 793	0
2 59	30 21	30 10	30 390	30 268	0 122	100	3 21	30 83	30 035	31 340	30 511	0 829	
3 00	30 21	30 11	30 405	30 292	0 113	94	3 22	30 88	30 055	31 405	30 545	0 860	
3 01	30 215	30 11	30 425	30 306	0 119	89	3 23	30 905	30 09	31 445	30 594	0 851	
3 02	30 22	30 11	30 445	30 320	0 125	85	3 24	30 925	30 11	31 480	30 628	0 852	
3 03	30 225	30 11	30 465	30 334	0 131	81	3 25	30 97	30 125	31 540	30 657	0 883	
3 04	30 23	30 105	30 485	30 343	0 142	77 5	3 26	30 995	30 15	31 580	30 696	0 884	
3 05	30 25	30 11	30 520	30 362	0 158	74	3 27	31 02	30 165	31 62	30 725	0 895	
3 06	30 275	30 11	30 560	30 376	0 184	71	3 28	31 04	30 19	31 655	30 764	0 891	
3 07	30 29	30 10	30 590	30 380	0 210	68	3 29	31 07	30 22	31 70	30 808	0 892	
3 08	30 297	30 09	30 612	30 384	0 228	66							

*Excess of R over L

Experiment 9—M C 2 45 p m volume of hands before armlets were put on, right 450 c c, left 444 c c At 3 00 p m blood-pressure determined with Riva-Rocci apparatus by stethoscope method Right arm At 122 sound began, at 92 began to decrease, at 82 disappeared completely Another observation At 95 sound began to decrease, at 82 completely gone Another observation At 124 sound began, at 98 became suddenly less, at 85 completely gone At 3 13½ p m hands put into bath with armlets on but no pressure Mouth temperature 36 7 C, rectal 37 05 C, pulse (sitting) 74 At 3 33½ p m hands put into calorimeters Between 3 43 5/6 and 3 44 p m established a pressure of 130 mm in left and 140 in right armlet (broad Riva-Rocci) Maintained pressure at 130 in left, and let it slowly sink in right At 4 05½ p m released pressure in both At 4 11½ p m hands taken out of calorimeters and dried Blood pressure again determined in right arm by Riva-Rocci with stethoscope, and with Erlanger method and stethoscope simultaneously At 122 sound began to be heard (this was also the systolic pressure by Erlanger record), at 98 sound suddenly began to

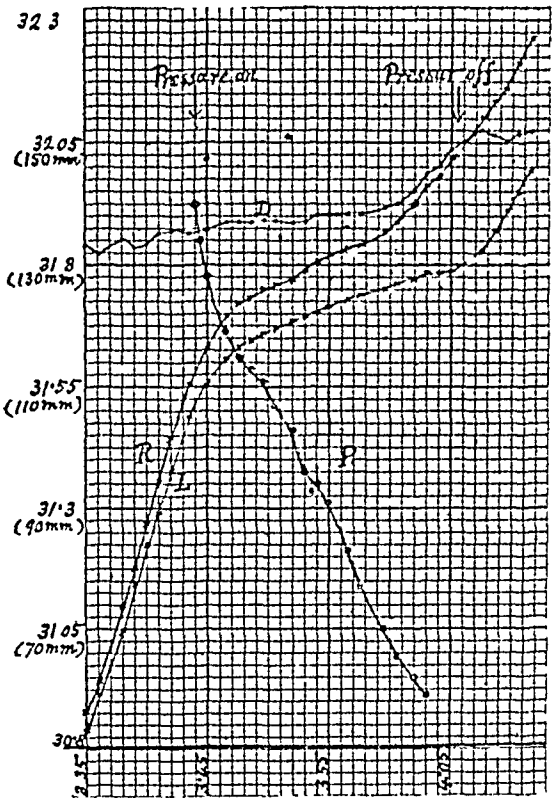

Fig 9—The letters have the same signification as in Figs 7 and 8, but the curves are plotted from Experiment 9

diminish, reappeared at 92, though not as loud as at first At 88 sound finally disappeared, and this corresponded to the diastolic pressure by Erlanger record Other observations gave 85, 86 and 92 as diastolic pressure by stethoscope method Volume of hands again measured after taking off armlets, right 486 c c left 461 c c

It will be seen at a glance, in Figures 7, 8 and 9, that as the pressure goes on diminishing in one armlet from the systolic pressure, the curves R and L, representing the rate of heat loss of the two hands to the calorimeters, remain practically parallel till the pressure has fallen very

TABLE 13.—RECORD OF CALORIMETER TEMPERATURES, EXPERIMENT 9

Time	Calorimeter Temperature					Pressure on Right Arm	Time	Calorimeter Temperature					Pressure on Right Arm
	Actual		Corrected					Actual		Corrected			
	R	L	R	L	Diff			R	L	R	L	Diff	
3 35.	30 88	30 84			0 04		3 54	31 615	31 53	31 805	31 704	0 101	94
3 36	30 93	30 91	30 94	30 919	0 021		3 55	31 62	31 53	31 82	31 714	0 106	91
3 38	31 07	31 02	31 10	31 048	0 052		3 56½	31 62	31 53	31 835	31 728	0 107	83
3 39	31 14	31 11	31 18	31 147	0 033		3 57½	31 615	31 53	31 84	31 737	0 103	77
3 40	31 22	31 18	31 27	31 226	0 044		3 59½	31 625	31 525	31 87	31 750	0 120	70
3 41	31 295	31 235	31 355	31 290	0 065		4 00½	31 635	31 53	31 89	31 764	0 126	65 5
3 42	31 375	31 31	31 445	31 374	0 071		4 02	31 655	31 525	31 925	21 773	0 152	62
3 43½	31 47	31 41	31 555	31 488	0 067	0	4 03	31 685	31 525	31 965	31 782	0 183	59
3 45	31 525	31 46	31 625	31 552	0 073	128	4 04	31 69	31 515	31 98	31 781	0 199	
3 46½	31 58	31 50	31 695	31 606	0 089	119	4 05	31 72	31 515	32 02	31 791	0 229	
3 47½	31 595	31 515	31 72	31 630	0 090	115	4 07½	31 78	31 53	32 105	31 829	0 276	0
3 48½	31 595	31 52	31 73	31 644	0 086	113	4 08½	31 80	31 565	32 135	31 873	0 262	
3 49½	31 605	31 525	31 75	31 658	0 092	111	4 09½	31 825	31 595	32 165	31 912	0 253	
3 50½	31 605	31 525	31 76	31 667	0 093	107	4 10½	31 86	31 62	32 215	31 946	0 269	
3 52	31 60	31 53	31 77	31 686	0 084	103	4 11½	31 90	31 655	32 265	31 991	0 274	
3 53	31 607	31 53	31 787	31 695	0 092	96	4 52	31 50	31 29				

considerably below the systolic pressure This is shown most clearly in the curve D, which depicts the difference in temperature of the two calorimeters at each point For a time it remains approximately parallel to the abscissa axis The first abrupt change in D, obviously indicating the point at which curves R and L begin to diverge sharply, corresponds to a pressure of 72 mm in Figure 7 (systolic pressure 118 mm), 77 5 mm in Figure 8 (systolic pressure 122 mm), and 77 mm in Fig 9 (systolic pressure 123 mm)

In Tables 14, 15 and 16 from the same three experiments the quantities of heat given off by the two hands are compared for the different pressures by taking the average for periods comprising several minutes Here also it will be noticed that the differences in the heat loss of the two hands experience the first really marked increase when the pressure in the right armlet is falling, in Experiment 7 from 67 to 61 mm , in Experiment 8 from 77 5 to 64 mm , and in Experiment 9 from 77 to 65 5 mm

The pressures at which the blood-flow is first notably increased in the observations in which the diminution of pressure in the armlet was produced abruptly by successive considerable decrements, agree very well

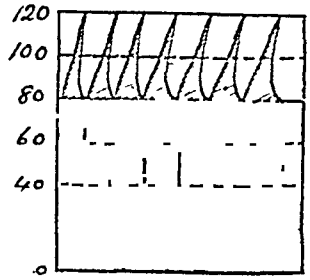

Fig 10 —For description see text

with the "critical' pressures obtained by the method of continuous escape The same is true of the critical pressure determined by raising the pressure in the armlet till the flow first begins to be seriously handicapped

It is easily understood why for some distance below the systolic pressure the increase in blood-flow should be inconspicuous Only the tops of the systolic waves are finding their way beyond the obstruction of the cuff, and the total flow in a given time is measured by the united areas inclosed between the tops of the curve and the horizontal lines representing the pressure in the cuff Thus in the diagram (Fig 10) the increase in the flow when the pressure is reduced from the systolic pressure, 120, to 100, is obviously slight Even with a diminution to 80 the combined areas represent less than half of the area of the rectangle formed by the lines 120 and 80 and the perpendiculars joining them A drop of 40 mm in the armlet from 80 to 40 will clearly produce a much greater increase in the flow than a drop of 40 mm from 120 to 80 This is on the assumption that the lumen of the arteries increases equally for equal decrements

TABLE 14.—HEAT GIVEN OFF BY HANDS IN EXPERIMENT 7

Period in Minutes	Heat Given Off (Small Cal.) per 100 c.c. Hand per Minute			Pressure in Armlet	
	R	L	Diff	R	L
6	32.70	40.70	8.00*	0	0
5	12.80	11.48	1.32	120-88	120
7	9.25	7.57	1.68	88-67	120
2½	12.60	7.06	5.54	67-61	120
5	13.35	6.18	7.17	61-55	120
8	13.56	3.31	10.25	55-50	120
8	16.44	3.86	12.58	50-40	120
10	8.95	24.43	15.48*	0	0

*Excess of left over right. The other numbers in this column are excesses of right over left.

TABLE 15.—HEAT GIVEN OFF BY HANDS IN EXPERIMENT 8

Period in Minutes	Heat Given Off (Small Cal.) per 100 c.c. Hand per Minute			Pressure in Armlet	
	R	L	Diff.*	R	L
7	48.43	42.57	5.86	0	0
3½	19.17	18.21	0.96	123-100	130
5	13.42	10.19	3.23	100-77.5	130
5	23.31	6.37	16.94	77.5-64	130
2	40.04	3.84	36.20	64-60	130
4	41.93	4.78	37.15	60-55	130
4	40.98	6.64	34.34	55-53	130
5	37.19	23.87	13.32	0	0
4	29.14	27.58	1.56	0	0

*Excess of right over left.

TABLE 16.—HEAT GIVEN OFF BY HANDS IN EXPERIMENT 9

Period in Minutes	Heat Given Off (Small Cal.) per 100 c.c. Hand per Minute			Pressure in Armlet	
	R	L	Diff	R	L
8½	60.52	58.95	1.57	0	0
3*	35.85	31.53	4.32	140-119	130
5½	10.34	11.18	0.84†	119-103	130
5½	9.74	7.04	2.70	103-77	130
3	12.74	6.98	5.76	77-65.5	130
2½	23.02	5.40	17.62	65.5-59	130
4	30.72	31.08	0.36†	0	0

*Pressure established in armlets only for the last 2½ minutes of this period.
†Excess of left over right, the other numbers in this column are excesses of right over left.

of external pressure, i e, for equal increments in excess of internal over external pressure, within the whole range of the pressures in question But MacWilliam[2] has shown that for excised arteries not in a state of continuous post-mortem contraction, the expansion when pressure is applied within the lumen is much greater in proportion to the pressure for the first increments of pressure than for further increments If we can assume that the arteries in the living arm are "soft" in the sense in which MacWilliam uses the term in the case of excised arteries relaxed by potassium sulphocyanid, or by keeping in blood at body temperature for twenty-four hours, we have an easy explanation of the fact that after the critical point has been reached removal of the first 40 or 50 mm pressure in the cuff produces a far greater increase in the blood-flow than removal of the second 40 or 50 mm Suppose the diastolic pressure is 90 mm Then when the pressure in the cuff is lowered from 90 to 70 mm the arteries are distended by a permanent excess of pressure of 20 mm A further diminution of pressure in the cuff of 20 mm i e, to 50 mm, corresponds to a permanent distending pressure of 40 mm within the lumen of the artery A further diminution of 20 mm in the armlet (i e, to 30 mm) corresponds to a distending pressure in the arteries of 60 mm In one experiment of MacWilliam the increase in cubic capacity of the artery (ox carotid) produced by increasing the internal pressure from 0 to 20 mm mercury was 14 (in arbitrary units), from 20 to 40, 13, i e, in all 27 for the first increment of 40 mm, while an increment of pressure from 40 to 60 mm caused an increase in cubic capacity of only 9, and from 60 to 80 mm an increase of only 8, or 17 in all for the second increment of 40 mm in the pressure The initial capacity of the piece of artery (17 mm long) would be 330 c mm, the lumen being 5 mm in diameter with zero pressure From the data given, which, however, are not quite complete for such a calculation, it may be reckoned that after the application of the first 40 mm pressure the capacity was increased to 520 c mm and the diameter to 6 3 mm, while after the second increment of 40 mm pressure the capacity was 640 c mm and the diameter 6 9 mm This is on the assumption that the capacity was increased mainly by an increase in the mean cross-section of the segment of artery without appreciable increase in its length, an assumption at any rate very likely correct for living arteries like the brachial opening up under the influence of the internal pressure as the pressure in the armlet falls Now by Poiseuille's law for tubes beyond the capillary size the volume of outflow varies as the cube of the diameter, i e, in the experiment in question the flows for the three conditions of the artery would be in the ratio 5^3 $(6.3)^3$ $(6.9)^3$ or 1 2 2.6 The second increment of 40 mm would therefore produce little more than half as great an increase in the flow as the first increment

2 MacWilliam Proc Roy Soc, 1901, lxx, 109

of 40 mm in the pressure, on the supposition that the flow through the arteries in the region of the block depends merely on the cross-section of the arteries and varies with the cross-section according to Poiseuille's law In our observations the difference would be much greater, for in MacWilliam's experiment the artery possessed so much rigidity that before pressure was established the lumen had a diameter of 5 mm, while in the living arm with a pressure in the cuff not less than the diastolic pressure, it can be assumed that they collapse completely after each pulsation

So far we have not taken into account the complicating factor that not only the arteries but the veins of the upper arm are compressed by the cuff It may be asked how do we know that the total block which we have demonstrated to occur with systolic pressure in the armlet is due to complete obliteration of the arteries and not simply to obliteration of the veins while the arteries still remain partially open? The answer to this is that the conclusions do not depend on observations made immediately after the establishment of the various pressures in the armlets If the arteries remain open with any given pressure and the veins are occluded, the pressure in the veins must eventually become equal to the arterial pressure, and blood will then again escape from the veins The handicap of the cuff, in so far as it consists in compression of the veins, will thus be overcome, and the flow, the veins having once been filled to their new capacity, will then again become steady, the same quantity of blood leaving the arm by the veins as enters it by the arteries As a matter of fact, Hill and Flack[3] have shown by actual experiment that when a pressure slightly below the systolic pressure is applied to the upper arm, the venous pressure in the forearm becomes equal to that in the armlet In a man with a systolic pressure of 220 mm, Hill applied a pressure of 200 mm to the arm and measured a venous pressure of 200 mm in the forearm He did not approach nearer to the systolic pressure because of the discomfort caused to the patient

In the observations which we have been discussing above it will be noted that the critical point in the falling armlet pressure, below which a further diminution of pressure is accompanied by a sharp increase in the flow, does not coincide with the diastolic pressure as measured by any of the clinical methods used but with a pressure usually about 10 mm lower In other words, the pressure in the cuff can be diminished 10 mm below the "diastolic" pressure without apparently rendering it sensibly easier for blood to pass through the previously compressed arteries A further diminution of the pressure in the armlet by 10 mm, however, leads to a distinct increase The most obvious suggestion is that the clinical methods of measuring diastolic pressure give somewhat too high a result But it

3 Hill and Flack Brit Med Jour, 1909 i 272, Proc Physiol Soc Feb 27, 1909 Jour Physiol, 1909, xxxviii 49 Hill, Heart 1909, i, 74

is possible that as our experiments necessarily involve a considerably longer compression of the arm than is practiced in clinical measurements of blood-pressure, the rigidity of the blood-vessels themselves or of the tissues immediately surrounding them, when the pressure begins to be reduced, is greater than normal, owing perhaps to increased tonic contraction of the vascular walls or edema of the tissues But the discussion of this question would lead us too far, especially as it is not necessary for the purposes of the present paper New data would also be required before it could be profitably considered

Certain practical applications of the observations described suggest themselves It is probable, e g, that in pathological cases measurements such as those given in Section II might throw light on the condition of the vessels as regards extensibility The response of the blood flow in the hands to handicaps of various amounts (below the diastolic pressure) applied to the arm might even be expected to give something of quantitative precision to such investigations In conditions of arterial hypertonus due to increased peripheral resistance a given handicap on the arm might be expected to produce a smaller relative diminution in the flow through the hand than with normal arterial pressure or in conditions of increased arterial pressure due to increased cardiac action, if such exist In certain cardiac lesions also it would seem that results of practical interest might be obtained by comparing the change in the flow through the hand produced by a given handicap on the arm with the effect produced in normal individuals In aortic insufficiency, for instance, it is to be expected that a greater diminution of pressure from the systolic pressure would be required to cause a sensible increase in the amount of heat given off by the hand than is normally the case, and the difference might afford some index of the degree of insufficiency Finally, the ease or difficulty, as tested by the volume of the circulation in the hand with which a given handicap is borne at different periods in the history of one and the same case, might afford information supplementary to that acquired by other methods, of progress or the reverse By the use of the foot calorimeters the method is, of course, equally applicable to the lower extremities

SUMMARY

SECTION I

It is concluded, on the basis of observations on two healthy young men, that a pressure equal to the systolic pressure, as estimated by the clinical methods used, applied to the upper arm by a broad cuff, causes complete cessation of the blood flow in the hand Since the pressure in the veins distal to the constricting armlet eventually becomes equal to the systolic arterial pressure, this is taken to mean that the lumen of the arteries under the cuff is actually obliterated

SECTION II

1 When the pressure in an armlet compressing the upper arm is reduced from the systolic arterial pressure the blood flow in the corresponding hand is only slightly increased for a considerable decrement of pressure

2 The pressure in the armlet must fall somewhat below the "diastolic" pressure, as clinically determined, before any marked increase in the flow through the hand occurs

3 The first decrements of pressure below this "critical" pressure are accompanied by a much greater increase in the flow through the hand than further equal decrements

4 A handicap of half the "diastolic" pressure causes only a relatively small diminution in the flow through the hand

5 It is suggested that the method of handicapping the circulation in the arm or leg by known pressures and observing in what degree the handicap is overcome, may in certain cases constitute a useful supplementary method of clinical investigation

A METHOD FOR THE MICROSCOPIC EXAMINATION OF GASTRIC EXTRACTS AND OF FECES

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Smears of gastric extracts or of emulsions of feces, as ordinarily made, generally return partial or unsatisfactory findings This is apt to be so when specimens are examined with an oil-immersion objective At the laboratory of gastro-enterology of St Mary s Hospital (Mayo Clinic) in an effort to make of greater worth the routine microscopic examination of gastric extracts particularly the procedure described below has recently been adopted

Advantage is taken of the opportunities offered by agar solutions recently emphasized by Ross[1] These may be combined with anilin dyes and chemicals to suit the work in hand

Agar Solutions—Two per cent agar solution is made by boiling up an appropriate quantity of best grade strip agar in distilled water The solution is filtered several times while very hot through double, hydrochloric-acid-washed filter paper On cooling it solidifies as a firm jelly It should be fractionally sterilized and refiltered on three consecutive days

For purposes of convenience, 5 c c of the molten agar are poured into each of numerous sterile test-tubes The tubes are plugged with sterile cotton and set aside at room temperature The agar jellies and may be used as desired

Stains—Thus far we have used coloring agents in combination with agar solutions for two purposes (1) for the differentiation of bacteria, blood-cells, epithelial elements, tissue-bits and the like, we have employed Unna's polychrome methylene-blue, Gram's mixture hematoxylin, thionin, methylene-blue (Loeffler's) and Wright's stain, (2) for the differentiation of starch residues, vegetable fibers, moulds, etc, we have employed freshly prepared Lugol's mixture

Procedure—For each specimen of gastric extract or feces emulsion, we make two agar-coloring matter combinations as follows The 2 per cent agar jelly is liquefied by heating over a Bunsen flame Two cubic centimeters of the solution are poured into each of two small test-tubes (those measuring 10 cm x 15 mm answer very well) Into each of the

*Manuscript submitted for publication March 29, 1912

1 Ross, H C Induced Cell Reproduction and Cancer, Philadelphia, 1911

tubes are then poured 15 drops of filtered staining agent For staining bacteria and the like we have found that Unna's mixture gives good results, while Lugol's solution colors starch elements better than simple iodin The added stains are intimately mixed with the agar and the tubes promptly placed in a beaker containing boiling water The agar is thus kept as a solution

Very thin smears of the gastric extracts or feces emulsions are made on cover slips It is desirable to avoid getting gross particles of food in the smears The smears may be dried in air or by rapidly passing through a gas flame

Onto the smear to be examined for microorganisms and allied elements, by means of a pipet with a 1 millimeter bore is placed 1 drop of the agar-methylene-blue mixture The cover slip is promptly inverted on a clean glass slide The agar-stain mixture rapidly spreads to the edges of the cover slip As it cools the agar solidifies, while the stain mixed with it permeates the smear Similarly, to the smear to be examined for starch remnants and the like, is added 1 drop of the agar-Lugol's mixture The cover slip is mounted at once on the same slide as the first preparation About two minutes suffice for firmly mounting and staining ordinary material In a series, the first preparations are ready for examination by the time the last are made

Examination.—The preparations are best examined by such light as comes from a Nernst, Schwann or tungsten lamp If electricity is not available a Welsbach mantle light suffices When the specimens are properly focused, using an oil-immersion objective, it will be seen that bacteria are stained blue or deep purple (Unna's mixture), blood-cells and nuclei are differentiated by pale pink and blue as are also epithelial elements, tissue bits, if small, may show atypical, mitotic cells. muscle fibers are pink to red with deeper striation mucus is in bluish strips or whorls Unless the preparation is overstained. vegetable fibers leptothrix moulds, etc, are but lightly colored In the smear prepared with agar-Lugol's mixture, vegetable fibers leptothrix, moulds, and starch remnants are appropriately differentiated The latter may be amethyst-blue, with deeper staining centers or laminæ reddish-pink with mahogany-colored centers or faint pink or colorless Budding yeasts moulds, and occasionally bacteria take a brownish-blue tinge Vegetable cells stand out prominently as blue to brown reticulum Large masses of amorphous material stain variously, but are readily distinguished from microorganisms

Uncolored Preparations.—The agar without coloring agents added may be advantageously used for mounting smears In fresh preparations when the smears are not dried motile organisms (bacteria protozoa) may be observed for a long time This is facilitated when the specimen is diluted with three volumes of warm normal saline solution before the smears are made.

ADVANTAGES OF THE METHOD

A routine, differential report on two dozen smears, from half as many specimens of gastric extracts or feces, may be made in about thirty minutes The specimens are simultaneously mounted and stained The solidification of the agar gives so firm a mount that the specimens may be examined with high or low power, with the stage of the microscope at any angle The mounting is sufficiently permanent to allow future study (we have preparations showing good fields after ten weeks) drawings, photomicrographs, or demonstration Comparison of the smears on the same slide, but differently stained, results in many interesting and instructive observations There would seem to be advantages in using the method for the observation of motile bacteria, protozoa, or cells with ameboid activity, when uncolored agar solutions are used

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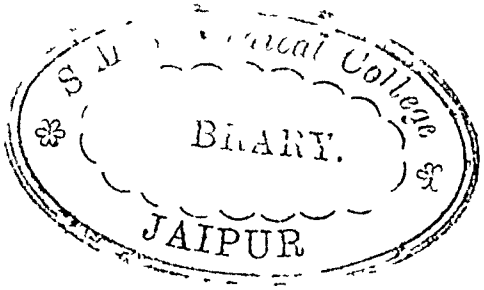
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